THE CONCEPT OF
ALANCED HOSPITAL COMMUNITY

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paper I shall consider two firmly rooted fea- our hospital tradition One is the separation of for the chronic and mentally sick from the gen- pitals The other is the concept of hospitals as structures, of more or less uniform design, each of provides a full range of services Both features origin to circumstances which no longer exist, would be considerable advantages in getting them.

separation of hospitals for the chronic and men- sick from the general hospital system is due to the formerly various classes of patients were regarded ent problems The infectious were to be isolated, tally ill were to be locked up, the chronic sick housed with the destitute, who were to be put to and only in the general hospitals was the idea of tion and treatment well established by the begin- the present century There was no conception munity of sick people, differing in age or in the of their illnesses, but with essential medical, nurs- social requirements in common In these cir- nces it was inevitable that the various classes of should be placed in different buildings, often ed by long distances and under different adminis- ns The 20th century has established the principle common standard of care and treatment, and the al Health Service has created a single hospital stration. We have yet to break through the thought which prevents us from realising that, if patients be separated, there is a far more satisfactory basis their age or the distinction between a physical and tal illness

inevitable consequence of the separation was the pt of a hospital as a single building providing a full of services, rather than as a group of buildings pro- complementary services It was necessary to make tals, so far as possible, self-contained In asylums poor-law institutions the standard of care was until tly so low that this requirement had little signi- ce, but in general hospitals it led to an attempt to able within every unit all the most complex resources edicine The general hospital has now become, in people's eyes, the model of what a hospital should nd attempts to improve the mental and chronic-sick tals are based on it.

we ignore the various subdivisions of the general tal system (obstetrics, paediatrics, chest diseases, and), hospital organisation is still based essentially on eparation of the mentally ill, the short-term physic- ll, and the long-term physically ill (identified mainly vanced age) To some extent this division is imposed e separation of existing buildings; but it is so deeply d in the tradition that it is still accepted in future ing It is a concept which has manifest disadvan- of which two are particularly serious It brings the same unit patients who need the full resources modern hospital and others who need only simple ion, or remain in hospital solely for social reasons And so long as they are isolated it seems impossible to staff adequately the mental hospitals and those for the chronic sick Indeed, so obvious are the disadvantages that small psychiatric and geriatric units are now sometimes included in general hospitals But the full implications of the traditional separation have still to be faced

Classification of Hospital Patients According to their Needs

Once it is recognised that the chronic sick should receive the same standard of medical care as the acute sick (or more accurately, since it is the real basis of separation, that older patients should receive the same standard as younger ones), and that patients who are mentally ill need not be separated sharply from those who are physically ill, one must conclude that the type of institution in which a patient is placed should be determined primarily by his needs An assessment of the needs of Birmingham patients in mental and chronic-sick hospitals (Lowe and McKeown 1949, Garratt, Lowe, and McKeown 1958) suggested that they could be divided broadly into four classes

1 Patients who needed full hospital facilities, such as frequent medical attention and skilled nursing

2 Patients who needed only limited hospital facilities—essentially simple nursing (washing, dressing, feeding, attention to bladder and bowel, &c.) without mental supervision.

3 Patients who needed only limited hospital facilities—essentially supervision because of their mental state, with (in a few cases) simple nursing

4. Patients who needed no hospital facilities, but remained in hospital chiefly for social reasons

The table gives the distribution between the four classes of Birmingham residents in mental and chronic-sick hospitals In this table patients in other types of hospital are grouped together on the assumption that they require full hospital care Actually, as was found in sanatoria (Lowe and Geddes 1952), not all of them do, but our data are not sufficient to enable us to say what the proportion is

On this assumption, that full hospital facilities are needed by all patients in general hospitals, the percentages of Birmingham hospital patients in each of the four classes listed above are 54, 9, 31, and 6 respectively Fig 1 shows the present location of these patients, and fig 2 shows the regrouping which would result from bringing together patients with similar needs

I do not, of course, suggest that all the patients in each class have identical needs, within each class there is con-

SUGGESTED REGROUPING OF BIRMINGHAM HOSPITAL PATIENTS ACCORDING TO THE TYPE OF FACILITIES NEEDED FOR THEIR CARE

Suggested regrouping of patients according to facilities needed	Present location of patients			Total	
	Mental* hospitals	Chronic-sick hospitals	General and all other hospitals	No	%
Full hospital care	459	309	4406†	5174	54
Limited hospital care without mental supervision	59	818	—	877	9
Limited hospital care with mental supervision	2596	309	—	2905	31
Hostel only	441	108	—	549	6
Total	3555	1544	4406	9505	100

*Patients in mental-deficiency institutions are excluded.
†It has been assumed that the patients now in general and other hospitals, for whom we have no data, all need full hospital facilities

Fig 1—PRESENT LOCATION OF BIRMINGHAM HOSPITAL PATIENTS

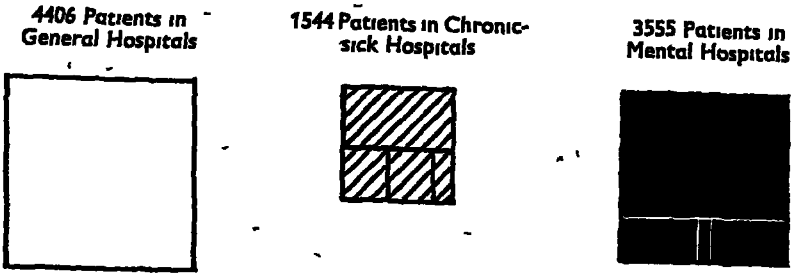
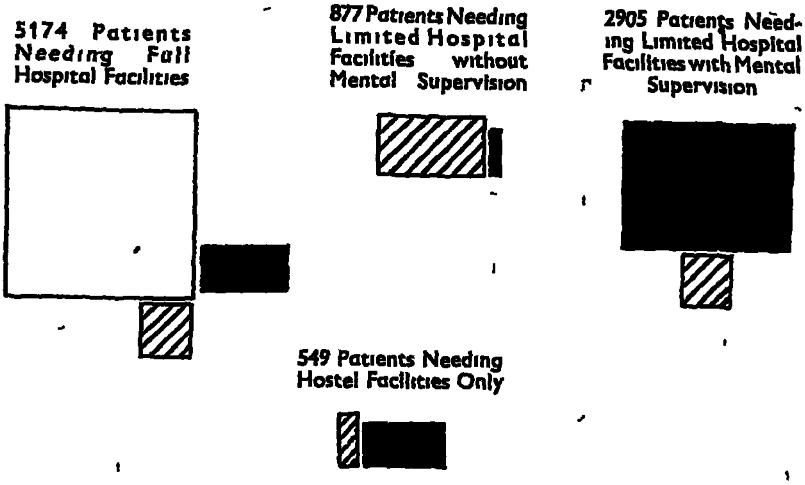


Fig 2—SUGGESTED REGROUPING OF BIRMINGHAM HOSPITAL PATIENTS



siderable scope for variation in type of accommodation and staff But as regards the facilities to be provided, the division here proposed seems the most fundamental, it brings together patients who, in terms of their hospital needs, have more in common with one another than with those in any other class

Advantages of a Common Site

So far we have been considering a regrouping of the present hospital population in order to bring together patients with similar needs If such a regrouping were effected, the resulting four classes could be accommodated either on different sites or on a common site I shall now consider the advantages of a common site in relation to administration, education, and research

Administration

One of the attractions of the National Health Service is that by creating a single administration it has exposed all types of hospitals to scrutiny according to a standard formerly applied only to general hospitals By this standard the services of mental and chronic-sick hospitals are still grossly deficient, and their deficiencies are not easily remedied The chief difficulty is to provide enough doctors and nurses It is conceivable that in years to come enough doctors may be forthcoming, partly because of increasing interest in psychiatry, and partly because of redundancy in other specialties But the nursing problem is unsolved, and under present arrangements is perhaps insoluble It derives basically from the fact that the nursing services as a whole already draw fairly heavily on the numbers of girls of a reasonable standard of education in the appropriate age-group An effective nursing service will need both a closer adaptation of training to function, on the lines suggested in the Nuffield report (Nuffield Provincial Hospitals Trust 1953), and a more equitable distribution of nurses between the various types of hospital In present circumstances they cann be redistributed, for whereas a doctor who could not find a niche elsewhere might be ready to serve in a mental or chronic-sick hospital, a nurse in the same circumstances would be more likely to leave nursing

So long as the mental and chronic-sick hospitals are separated from the gener hospitals, they must depend on recruitment of nurses and doctors prepared devote themselves exclusively to the services, and the difficulties will remain The difficulties can, I believe, be over come only by placing these hospitals close enough to the general hospitals to make it possible for the same staff to serve both Most doctors and nur would be willing to make a contributio to the care of the mentally ill and th chronic sick if it could be reconcile with their other work, but they will no do so if it obliges them to cut themselve off completely and permanently from their main interests

A second administrative advantage o a common site is that it would provid far greater flexibility in the use o buildings and staff In some specialties need are changing rapidly, and it is almost impossible to say what they will be in ten or twenty years' time For example, it is possible, though hardly certain, that advances in therapy and improved outpatient and domiciliary care will greatly reduce the size of the mental-hospital population

In these circumstances it seems vital that buildings should be so sited that if they are not needed for their original purpose they can readily be converted to other uses This is impossible so long as major sections of medical work are isolated It would be relatively easy if they were all on the same site

Education

To a very considerable extent the decision of doctors and nurses about their future work is determined by wha they see and hear in the hospitals where they are trained Unfortunately patients in teaching hospitals, and in the non-teaching hospitals in which schools of nursing are usually located, are very unrepresentative of the tota hospital population Inevitably students conclude tha the work of general hospitals is the chief interest of doctors and nurses, and that, apart from a few eccentric with a sense of vocation, no-one works in a mental o chronic-sick hospital if he can possibly do anything else This interpretation cannot be altered by token visits to outlying hospitals, which are as likely to harden a determination never to set foot in them again

To recognise this difficulty is not necessarily to question the advisability of basing training on general hospitals, or to suggest that the type of patient admitted should be changed Indeed, if the only way in which the hospital population available for teaching purposes could be made more representative were to admit long-sta mentally ill and chronic-sick patients to the general wards it could well be argued that the disadvantages would outweigh the advantages But the grouping of hospitals with complementary services on a common site is an entirely different proposal patients would be housed in buildings designed after close examination of their needs What is important for teaching is that the student doctor and nurse should see something much nearer to a cross-section of the whole hospital population, in circumstances in which they recognise that all types of patients are equally acceptable as a medical responsibility and interest

Research

Confronted for the first time with the existing arrangements in research, an observer might be excused for concluding that, through some unfortunate error in casting, the ablest workers had been assigned to the easiest problems The reasons for this situation are complex, but certainly one of them is that administrative arrangements determine what the research-worker sees, and what he sees has a considerable bearing on what interests him A physician who admits to his wards only acutely ill people is unlikely to be much concerned with the chronic sick, and a psychiatrist preoccupied with short-term treatment or mendelian inheritance cannot be expected to think constantly about the chronic psychotic Not least of the advantages of having all facets of medical work on a single site is that it would bring some of the thorniest and socially most important problems to the attention of the ablest workers It can hardly be doubted that the slow advance with these problems hitherto has been partly due to their isolation

A Balanced Hospital Community

Having considered the advantages of assembling the various elements of the hospital system on a single site we may now examine some of the implications of such a policy I must first state the proposal as clearly as possible What is suggested is that hospitals should be planned as a group of buildings with a common medical and nursing staff providing complementary services for all classes of patients, rather than as single buildings providing a full range of services for selected groups The buildings would be of varied size, design, and permanence of structure, each closely adapted to the needs of the patients who would occupy them

There can be little doubt that if architects were given the opportunity to apply to such a hospital community the imaginative treatment which has been so successful elsewhere, the results would be equally attractive Ideally the community would not be isolated, at its centre there would be careful siting of buildings and control of traffic, but at its periphery it would merge with the neighbourhood which it served By avoidance of large buildings, and by inclusion of other amenities—shops, amusements, and so on—a domestic rather than an institutional setting could be created In these circumstances the analogue of the hospital would no longer be the somewhat forbidding block of flats, but the well-planned housing estate or university centre

If this proposal is not to be dismissed as romantic and unrealistic, we must consider at least two possible objections One is that the capital and maintenance costs would be excessive The other is that, however attractive such a setting might be to the architect or planner, its amenities would bear little relation to the real needs of the hospital population

It is true, of course, that a considerable capital outlay would be required to establish such a centre But there are several reasons for thinking that in relation to the services provided the costs would be lower than those of the traditional hospitals

(a) There would be no duplication of expensive facilities or mixing of patients with different needs

(b) Three of the four major units (see diagram) could be of cheap construction

(c) Because of the relatively simple conversion of unwanted facilities to alternative use, there would be little waste

The last is a particularly important consideration in a period when numbers and types of patients may change rapidly The trimmings which could contribute so much to the creation of a domestic atmosphere—shops, restaurants, and amusements—could operate on the usual commercial basis, and with a favourable site in relation to a large resident population there is no reason to suppose they would not do so Nor need we suppose that maintenance costs must be excessive

The objection that the amenities would bear little relation to the real needs of hospital patients derives from failure to appreciate the true nature of the whole hospital population For the acutely ill bedfast patient who is retained for a few weeks, the general character of the area in which he is cared for is perhaps of secondary importance But a substantial part of the hospital population is ambulant, and the period of admission is measured in years rather than days It is for these patients that the character of the area and the nature of its general amenities are so important At the very least they would provide a more attractive environment in which to spend a long period, and in the case of the mentally ill it is not too much to expect that they would make a considerable contribution to recovery

Possibilities Where Planning is Restricted by Existing Hospitals

Another possible criticism of the idea of a balanced hospital community is that however desirable it may be, and however practicable in countries such as India or Ghana where the planner can work on a virgin site, it has little bearing on the problems of areas where planning is restricted by existing structures In the British Isles for a long time we shall have to make do with the present hospitals, however unsuitable in design, and many of the available sites, particularly in urban areas, are so small that they could not accommodate a balanced community

Nevertheless, though the transformation of the hospital centre may be slower than we might like, it seems essential to have in our minds a model of what it ought to be in future For while we must accept the limitations imposed by an earlier tradition, we need not increase the difficulties by continuing to build within that tradition Almost every major development within the service would be influenced in some degree by a decision that hospitals should no longer be planned as isolated structures of uniform design In the planning of a general hospital, for example, it would affect both the location and size of the site, and the design of the building itself would be different if it were to accommodate those of the mentally ill and the aged sick who need the full resources of a modern hospital It would be evident that at all costs the isolation of hospitals for the mentally sick and chronic sick should be avoided

Summary

An analysis of the medical and nursing needs of Birmingham hospital patients showed that they could be grouped into four classes, according to whether they required (a) full hospital facilities (54%), (b) limited hospital facilities, consisting of basic nursing without mental supervision (9%), (c) limited hospital facilities, consisting of mental supervision with little basic nursing (31%), and (d) no hospital facilities (6%)

Considerable advantages would result from planning hospitals as a group of buildings with a common medical and nursing staff providing complementary services for all classes of patients, rather than as single buildings providing a full range of services for selected groups

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POSTOPERATIVE METABOLIC CHANGES IN RELATION TO NUTRITIONAL REGIMEN *

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PREVIOUSLY we presented evidence indicating that postoperative wasting of protein and loss of body-weight can be minimised or prevented by giving intravenously a solution containing 5% protein hydrolysate and 10% hexose in conjunction with a fat emulsion or an anabolic hormone (Abbott 1955, Abbott et al 1953, 1955, 1957 a and b, Holden et al 1957, Krieger et al 1957, Levey et al 1957) Since there is still some controversy about the use of these preparations, we have tried to obtain more conclusive data

We believed that the relative importance of nutrition and operative trauma in influencing postoperative metabolism could be estimated by comparing the metabolic response of the patient to the same intravenous regimen during a three-day control period and subsequently during a three-day postoperative period To restore the patients to a nutritional state comparable to that which existed before the control period they were given an adequate oral intake for three or four days before the operation In this manner it should be possible to differentiate the metabolic alterations induced by surgical trauma from the biochemical changes resulting solely from the various nutritional regimens The metabolic alterations were assessed by comparing the changes in weight, along with sodium, potassium, and nitrogen balance and the urinary excretion of 17-hydroxy-corticoids during the three-day control and postoperative periods Moore et al (1955) and Steenburg et al (1956) have stated that there is a correlation between the cumulative nitrogen balance and the urinary 17-hydroxycorticoid output for the first four postoperative days It is also generally believed that there is an obligatory retention of water and sodium and a deficit of potassium postoperatively The validity of these concepts was further investigated

Methods

Eleven women and two men about to undergo an elective cholecystectomy were admitted to the metabolic division of the University Hospitals of Cleveland so that accurate observations could be made These patients were given one of the three following regimens in the three-day control and postoperative periods

Group A —Three women (fig 1) and two men (fig 2) were given only 5% dextrose in water intravenously

Group B —Four women (fig 3) were given only 5% dextrose in water to which had been added about 90 mEq of sodium and 80 mEq of potassium daily

Group C —Four women were given 5% protein hydrolysate in a 10% fructose solution † to which sodium and potassium were added to provide a daily intake of 90 mEq of sodium and 80 mEq of potassium

The intravenous infusions were started between 8 A M and 9 A M and regulated so that the patients received 500 *ml* per hour All excreta were collected and analysed for sodium, potassium, and nitrogen by methods previously described (Abbott et al 1953) The daily urinary excretion of 17-hydroxycorticoids determined by the method of Glenn and Nelson (195 To determine accurately the daily changes in the bo weight the patients were weighed at 6 30 A M voiding and at least eight hours after taking any food or fluids

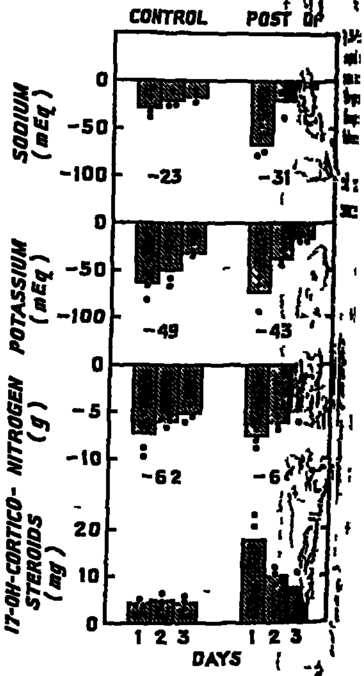

Fig 1—Metabolic balances for sodium (mEq), potassium (mEq), and nitrogen (g) and daily excretion of 17-hydroxycorticoids in 3 female patients receiving 5% dextrose in water during control and postoperative periods

The length of the sodium, potassium, and nitrogen histograms represents average daily balance for 3 patients, and the dots represent the individual daily values for each patient. The numbers below the balance charts represent the average balance in mEq. daily for sodium and potassium and in g daily for nitrogen in the 3 patients during the control and postoperative periods

Results

The data obtained in studying the patients in group (figs 1 and 2) show that the deficits of sodium, potassium,

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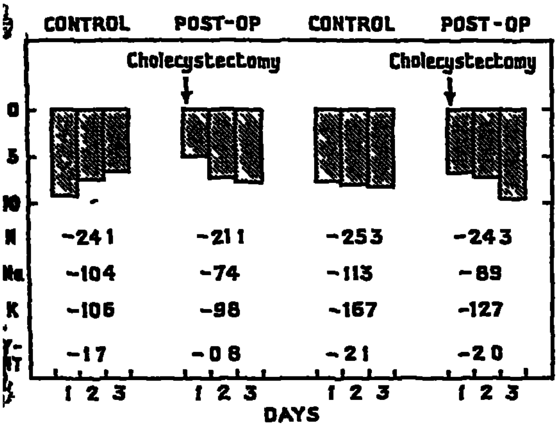
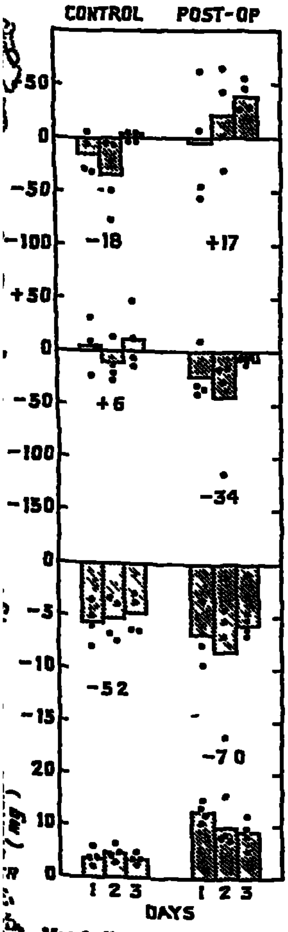
* This paper is the twelfth of a series on Metabolic Alterations in Surgical Patients The work was supported in part by grants from the National Institutes of Health, U S Public Health Service A-760(C5), the John A Hartford Foundation, Baxter Laboratories, Morton Grove, Illinois, and the Mead Johnson Co, Evansville, Indiana

† 5% 'Amigen' (enzymatic protein hydrolysate) in 10% 'Levu (fructose) supplied by Mead Johnson & Co



—Metabolic balances in 2 men, aged 75 and 67, during 3-day trol and 3-day postoperative periods Patients were given amounts of 5% dextrose in water during both periods ogen balance (g), cumulative 3-day nitrogen balance (g), nge in body-weight (kg), and cumulative sodium and potassium ances (mEq), are shown for each period.

nitrogen were not appreciably influenced by sthesia and uncomplicated cholecystectomy



The greatest sodium deficits were observed on the first day of each study period and were followed by a gradual conservation The three women showed postoperative deficits that were slightly greater than those noted in the control period On the other hand, the two men showed slightly greater sodium deficits during the three-day control period than they did postoperatively We think that these slight variations are not significant, and that the deficits of sodium in the control and the postoperative periods can be regarded as comparable

Although there were slight variations in the extent of the cumulative deficits of potassium and nitrogen and loss of body-weight for the control and postoperative periods, the alterations were related primarily to the diet and were not appreciably influenced by the operation The average *daily deficit* of nitrogen was 6 4 g postoperatively for the three women (fig 1) and 7 6 g for the two men (fig 2) in group A These deficits are similar to those exhibited by one healthy woman and two healthy men maintained for three days on a diet similar to that given to the patients in group A The woman had an average *daily nitrogen deficit* of 5 3 g and the men 8 0 and 8 2 g (Holden et al 1957)

—Metabolic balances for sodium, potassium, and nitrogen daily excretion of 17-hydroxycorticoids in 4 female patients ceiving 5% dextrose in water containing about 90 mEq of dium and 80 mEq of potassium during control and post-perative periods

The length of the sodium, potassium, and nitrogen histograms ents the average daily balance for the 4 patients and the *dots* resent the individual daily values for each patient. The numbers w the balance charts represent the average daily balance for each iod.

The remaining eight women (groups B and C) received daily about 90 mEq of sodium and 80 mEq of potassium

The sodium balances of the four women in group B (fig 3) varied only slightly above and below equilibrium, the oldest women (aged 61), who postoperatively showed a three-day cumulative positive balance of 175 mEq of sodium with a three-day intake of 258 mEq of sodium With the exception of this patient, fluctuations of sodium balance during the postoperative period were not unlike those observed in healthy people on a constant diet

There were only slight deviations from equilibrium in potassium balance in both the control and postoperative studies, if one excludes the data obtained from one patient who developed a wound infection during the postoperative period She had pyrexia (100 4–102 2°F) for the first five postoperative days This patient's cumulative postoperative three-day deficits of potassium and nitrogen were 160 mEq and 33 g respectively These deficits are considerably greater than those noted for the other patients in this group and are attributed to the postoperative complication rather than the operative stress If the data obtained from the study of this one patient are excluded, the average daily postoperative deficits of potassium and nitrogen of the remaining three patients in group B were 15 mEq and 5 7 g respectively, which are comparable to that of the female volunteer and the patients *in group A*

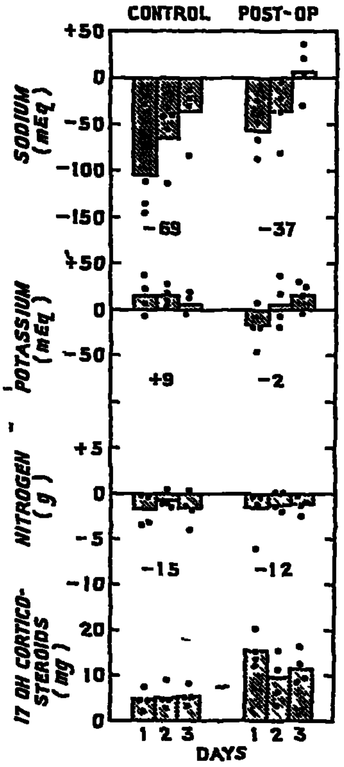


Fig 4—Metabolic balances for sodium, potassium, and nitrogen and daily excretion of 17-hydroxycorticoids in 4 female patients given a solution of 5% protein hydrolysate containing 10% fructose and about 90 mEq of sodium and 80 mEq of potassium

The length of the histogram represents the average daily balance for the 4 patients, and the dots represent the individual daily values for each patient. The numbers below the balance charts represent the average daily balance for each period

The deficits of nitrogen during their control periods (fig 3) are somewhat more difficult to explain Two of the patients showed average daily nitrogen deficits during the control period of only 3 2 g and 4 1 g Such low nitrogen values are not often observed for at least several days after a healthy person is changed from a normal diet to a 500-600-calorie protein-free diet

Thus, measured by sodium, potassium, and nitrogen balances, the postoperative metabolic response of the three patients in group B who had no complications was essentially the same as that of the patients in group

A and the three healthy volunteers in the control period.

The metabolic alterations in the control and postoperative periods of the patients in group C, who received 5% protein hydrolysate in a 10% fructose solution with electrolytes, are shown in fig. 4. The deviations from equilibrium of potassium and nitrogen were less than those shown by the patients in the two other groups. Though their sodium balances varied somewhat, most of the patients showed smaller sodium deficits during the postoperative period than during the control period. The urine volumes were largest in this group who received the protein hydrolysate. The potassium intake was adequate to maintain these four patients, who received a modest amount of protein and calories, close to equilibrium. These four patients lost less body-weight than those who were not given nitrogen and had received only 500–600 calories from the intravenous dextrose (groups A and B). The fact that the patients in group C lost some weight and showed a nitrogen deficit during the control period probably indicates that the caloric intakes of these patients were suboptimal during both the control and the postoperative periods.

All the patients showed a fairly abrupt increase in the urinary excretion of 17-hydroxycorticoids on the day of operation or the first postoperative day. Over the next two to four days these values gradually returned to normal. The cumulative urinary 17-hydroxycorticoid values for the three-day postoperative periods were 50–250% above the values obtained during either the control or the repletion periods. The increase in the urinary excretion of 17-hydroxycorticoids showed no correlation with the postoperative sodium, potassium, or nitrogen balances.

Two patients, who received only dextrose in water, had almost identical postoperative three-day cumulative nitrogen deficits. However, the postoperative increase in the urinary 17-hydroxycorticoids in one of these patients was considerably greater than in the other. One of the other patients, who was given 5% protein hydrolysate in a 10% fructose solution during the control and the postoperative periods, was essentially in nitrogen equilibrium before and after operation. The postoperative increase of urinary 17-hydroxycorticoids of this patient was comparable to that shown by many of the other patients who had greater nitrogen deficits.

It is clear from these studies that the intravenous infusion of a suitable protein hydrolysate, when supported by adequate calories, will either minimise or prevent postoperative wasting of nitrogen and loss of weight, if complications are avoided.

Discussion

The data obtained from this study substantiate our previous findings, that operative trauma and anæsthesia per se are only minor factors in determining the pattern of the metabolic response to surgery. The major factors are the dietary regimens, the complications, the previous nutritional state, and the sex of the patient. We believe that the impression gained by other workers that the postoperative metabolic alterations are obligatory is derived largely from studies in which an insufficient amount of calories, little or no nitrogen, or a nutritionally inadequate protein hydrolysate was given.

In analysing data which we obtained from the study of other patients we have been impressed by the large losses of nitrogen, potassium, and body-weight when extensive blood-loss, necrotic tissue, or serious infection is present. When the intake of calories and protein is adequate, these nitrogen and potassium deficits can often be minimised but may continue until the blood-loss is at least partiall corrected, necrotic tissue removed, or infection controlled.

After operation there is an increase in adrenal activit measured by the urinary output of 17-hydroxycorticoids. These hormones are desirable and are necessary in th resistance to injurious processes and help to maintai homœostasis. The endocrinological response to cholecystectomy in these patients was insufficient to caus changes in the sodium, potassium, and nitrogen balanc from those noted during the control period. Aldosteron and adrenal steroids may often be liberated because of a inadequate intake of various nutrients or because injur has produced physiological changes or variations in bod chemistry. The 17-hydroxycorticoids, like other hormone may help to make available or conserve certain needed substances which influence cellular metbolism or permeability and thus help to tide the injured organism over a period o stress. Increased amounts of antidiuretic hormones an aldosterone are made available when water and sodium are withheld from healthy people. Thus the liberation o such substances after injury or after an elective operatio indicates that the body is conserving water or salt or both. Therefore judicious amounts of these substances shoul be given. We believe that the postoperative metaboli derangements should not necessarily be regarded as bein caused by the increased endocrine activity but, rather, that the output of the various hormones may largely result from the physiological and biochemical change caused by treatment and injury. Our findings lend additional support to the concept of "permissive activity" of the adrenal steroids as postulated by Ingle (1952, 1954 and supported by others (Conn et al. 1954, Engel 1952).

Conclusions

By providing adequate nutrients during the early postoperative period the restoration to a normal state can be aided rather than hindered. Adequate nutrition may also decrease the magnitude of the endocrine response after operation.

✓ There was no correlation in this study between the nitrogen or electrolyte balance and the amount o 17-hydroxycorticoids excreted in the urine.

These studies indicate that, after an uncomplicated operation, the usual patient who does not have extrarenal losses should get daily 75–125 mEq. each of sodium and potassium. Such intakes should maintain a sodium and potassium balance near equilibrium or prevent appreciable deficits and excesses.

✓The loss of weight and wasting of nitrogen and potassium shown by the adult patient who is in an adequate state of nutrition after an uncomplicated elective operation are not obligatory but are primarily the result of the diet he has been given.

The occurrence and severity of postoperative complications are important factors influencing the magnitude of the metabolic response to operation. Though infection, hæmorrhage, tissue damage, &c., may greatly increase the caloric needs and accelerate the metabolic processes, these effects can be minimised by an adequate intake of calories and protein. It is essential, however, that any infection be controlled, necrotic tissue removed, and blood-loss corrected before these alterations due to complications can be eliminated.

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SERUM-LIPIDS AND BLOOD-SUGAR LEVELS IN CHILDHOOD DIABETES

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THERE is wide agreement that the serum-lipoprotein rises before the development of atheroma (*Circulation* 1956), but it has not yet been proved that the rise causes the disease (Ahrens et al 1957) Less agreement exists about the precise lipoprotein fraction or fractions increased before atheroma

In diabetes mellitus there is a well-recognised tendency for arterial disease to develop prematurely, leading to occlusive coronary disease, retinopathy, or nephropathy It is uncertain to what extent these complications are preventable by strict diabetic control

We have studied the serum-lipids and serum-lipoproteins in diabetic children Though our patients showed no clinical evidence of arterial disease, they must be regarded as almost certain candidates for its development (White 1949), and therefore presented an opportunity for us to define the lipoprotein abnormality in the pre-atheromatous diabetic patient We have also considered that abnormality in relation to such other factors as blood-sugar level, age, and duration of diabetes

Patients and Methods

A study was first made of the levels of lipids and of lipoproteins in the serum of 35 children attending the diabetes clinic

Our diabetic regime includes a diet wherein only the carbohydrate is regulated, but an ample supply of carbohydrate is allowed—e g, 200–250 g for a child aged 8/10 years All the children receive a single injection of insulin-zinc suspension twenty to thirty minutes before breakfast Blood for analysis was taken at a routine monthly visit to the clinic, neither parent nor child knowing beforehand that any special test would be applied The clinic takes place in the afternoon, hence the blood was obtained two or three hours after the main meal, which contained 50–70 g of carbohydrate This explains why in many patients the blood-sugar level was high, even though the patients were all in good health and clinically free from diabetic complications, and routine examinations of urine in the patients' homes every morning and night usually indicated good or fair diabetic control

Serum-lipoprotein was separated [illegible]trophoretically on absorbent paper into omega, beta, and alpha [illegible]ions, after staining with oil red O, the total lipid and the fractio[illegible]ere estimated by the method described by Salt and Wolff (1957) The usual normal values are included in table II

Analyses of sera for total cholesterol (Sackett 1925), total esterified fatty acid (Stern and Shapiro 1953), and lipid phosphorus (method adapted from Gomori 1942) were also made.

Blood-sugar values were estimated by the Folin-Wu micro-technique, using unlaked blood in Herbert and Bourne's method (Harrison 1937)

In calculations a representative molecular weight of 277 2 was used for fatty acid, phospholipid (M.W 806) was obtained by lipid phosphorus × 26

We regard as conventional normal ranges for children cholesterol 20–250, esterified fatty acid 190–450, and phospholipid 160–310 mg per 100 ml of serum

Results

Scrutiny of the individual results from the 35 diabetes-clinic (treated) patients showed that only a few values for total lipid, beta-lipoprotein, esterified fatty acid, and cholesterol were above the normal range Slightly raised levels of phospholipid were common, but here, as with other serum-lipid components, doubt exists about the precise extent of the normal ranges

The analytical data were then collected into two subgroups according to the patients' blood-sugar level—A, below, and B, above, 200 mg per 100 ml A summary of the results is given in table I, together with the values for t and P (Fisher 1941), which furnish a statistical value of the magnitude and significance of the differences between the means

The two subgroups are not distinctive in age-distribution, insulin dosage, or duration of diabetes There is a trend in subgroup B toward a larger amount of total lipid in the serum Of the three lipoprotein-lipid fractions the beta-fraction exclusively is significantly larger in subgroup B The levels of cholesterol and of total esterified fatty acid in the serum are also significantly higher in subgroup B, but phospholipid shows no significant difference between the two groups

To study more closely the correlation between the lipoprotein-lipid fractions and the blood-sugar level, the results were divided into five groups according to the patients' blood-sugar levels (up to 100 mg per 100 ml, 100–200 mg and so on), and for each group mean values for the lipoprotein fractions were calculated The results of this analysis (fig 1) show a progressive rise in the beta-lipoprotein lipid with each incremental step in the blood-sugar level in the higher ranges of blood-sugar In contrast the alpha and omega fractions show no variation in relation to blood-sugar

No relationship was apparent between any other factors, such as age of patient, degree of diabetic control assessed by long-term review, and the several serum-lipoprotein fractions

Serial Observations in Individual Patients

Our first studies were based on the examination of a group of diabetic children all in good or fair control In further studies we have attempted to determine whether the correlation between certain serum-lipids and blood-sugar levels exists also in the individual diabetic patient.

Besides the method already described, the level of total lipid in the serum was also estimated by the method of de la Huerga et al (1953) Usually the results by the two methods were in fairly close agreement, on the few

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TABLE I—SUMMARY OF CLINICAL DATA AND LABORATORY FINDINGS FOR 35 CHILDREN WITH DIABETES MELLITUS

Clinical data and laboratory findings (mg per 100 ml except where otherwise stated)	Blood-sugar level								Statistical assessment of differences between means*	
	A, below 200 mg per 100 ml (13 patients)				B, above 200 mg per 100 ml (22 patients)					
	No of observations	Range of values found	Mean value	S D	No of observations	Range of values found	Mean value	S D	t	P
Patients' age (yrs)	13	3–13	9 6	3 07	22	4–13	9 9	2 98	0 29	0 8
Daily insulin (units)	13	8–128	59	36	22	16–136	52	29	0 58	0 6
Duration of diabetes (yr)	13	1 0–7 0	3 0	1 97	22	0 5–11 0	4 6	3 36	1 56	0 15
Serum-lipoprotein lipid										
Total	13	368–907	635	140	22	490–1176	730	179	1 73	0 1
Omega fraction	13	19–228	101	65	22	25–204	97	45	0 21	0·9
Beta fraction	13	217–617	340	101	22	254–741	427	138	2 04	0 05
Alpha fraction	13	85–345	194	67	22	112–295	206	50	0 61	0 55
Beta/alpha ratio	13	1 1–4 5	1 97	0 98	22	1 1–4 4	2 18	0 81	0 68	0 5
Serum-total cholesterol	11	93–240	159	41	18	114–306	213	46	3 18	0 01
Total esterified fatty acid	12	175–422	270	81	21	177–637	358	137	2 03	0 05
Phospholipid (as lecithin)	12	179–629	314	129	20	166–593	327	117	0 29	0 8

* Values of P—0 05 or less indicate significant differences between the means

occasions (mainly high levels) when there was substantial disagreement the estimations of total lipid by de la Huerga's method were preferred These were regarded as the more correct on evidence from computations made by summation of the levels of esterified fatty acid, cholesterol, and glycerophosphoryl-choline (phospholipid residue) in the serum

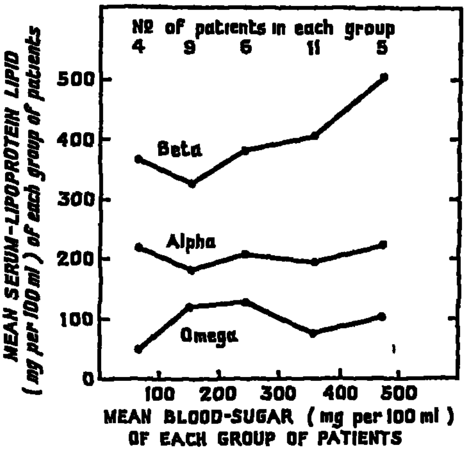

Fig 1—Relationship between mean blood-sugar level and mean level of lipoprotein-lipid fractions in serum of diabetics under control Each mean value is derived from a number of patients grouped by blood-sugar ranges up to 100, 100 to 200, &c , mg per 100 ml

Three previously untreated diabetic children were examined before and at various intervals after the start of insulin treatment In addition, one diabetic girl, previously under treatment, was studied both in diabetic coma and during her recovery, which was delayed by the development of peripheral neuritis and gangrene

In the following case-reports only the salient features are mentioned The laboratory findings in the four cases are presented in table II

Case-reports

Case 1—A girl, aged 6 years, developed symptoms of diabetes mellitus in *March*, 1957 On admission to the Children's Hospital in May, 1957, her general condition was fair, and she was fully conscious and only slightly dehydrated Her urine contained sugar (2 g per 100 ml) and ketones The carbon-dioxide combining power of the serum was 43 volumes % (19 mEq per litre) The levels of blood-sugar, serum-total lipid, and serum-beta-lipoprotein before and for forty hours after the institution of insulin treatment are shown in fig 2

A greatly increased amount of beta-lipid was mainly responsible for the initially enormous increase in the total lipid, within twenty-four hours of the start of treatment the beta fraction had fallen to within normal limits It is particularly important to note that the precipitous fall of the blood-sugar level to 31 mg per 100 ml which followed the first injection of insulin (20 units) was accompanied by an equally rapid fall of the level of the beta-lipoprotein fraction

Case 2—A girl, aged 11 years, developed symptoms of diabetes mellitus in February, 1957, and was admitted to hospital in June, when she was found to be very thin, with a dry skin, she was fully conscious Her urine contained glucose (2 g per 100 ml) but only a trace of ketones, acidosis was only moderate, with a carbon-dioxide combining power of 37 volumes % (16 5 mEq per litre) Again the beta-lipoprotein level quickly returned to normal, though not quite so rapidly as in case 1

Case 3—A girl, aged 3 years, developed symptoms of diabetes mellitus in October, 1957, three weeks later, on *admission to hospital, she was fully conscious* and moderately dehydrated, and her urine contained glucose (2 g per 100 ml) and ketones In this child, although ketosis was abolished during the first day of insulin treatment, the fall in blood-sugar level was only slight, and correspondingly the fall in serum-beta-lipoprotein level was slight

Case 4—A girl, aged 12 years, who had developed diabetes mellitus at the age of 3 years, was readmitted in December, 1956, in diabetic coma, with a serum carbon-dioxide combining power of 15 volumes % (7 mEq per litre) After a stormy course her condition improved, but then she developed peripheral neuritis and gangrene of a toe A second specimen of blood was examined four and a half months later, when those complications were still present It is important to note that the lipoprotein

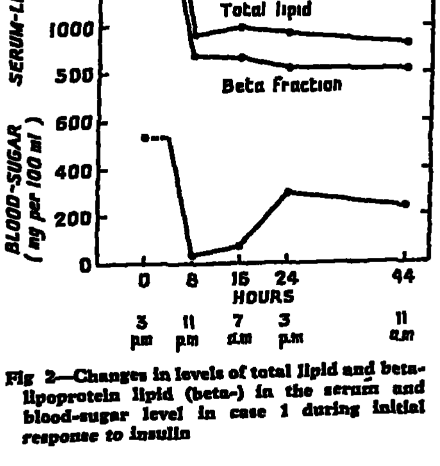

Fig 2—Changes in levels of total lipid and beta-lipoprotein lipid (beta-) in the serum and blood-sugar level in case 1 during initial response to insulin

TABLE II—SERIAL OBSERVATIONS ON THREE INITIALLY UNTREATED PATIENTS AND ON A PATIENT WHO DEVELOPED DIABETIC COMA

Case no.	Age (yr.)	Time of observation	Clinical state	Blood-sugar (mg. per 100 ml.)	Serum-lipid and lipoprotein-lipid fractions (mg. per 100 ml.)				Ratio beta/alpha	Position of beta-L.P. peak and character of beta-L.P. band*
					Total	Omega	Beta	Alpha		
1	6	0 hours	Untreated	534	2560	333	1997	230	8·7	Advanced*
		8 „	4 hr. after 1st insulin	31	900	63	684	153	4·5	Advanced*
		16 „		71	990	109	673	208	3·2	Advanced*
		24 „		300	920	221	561	138	4·1	Advanced*
		44 „		242	820	82	549	189	2·9	Normal*
2	11	0 hours	Untreated	935	1010	111	727	172	4·2	Advanced
		4 „	3 hr. after 1st insulin	273	1020	112	704	204	3·5	Advanced
		16 „		232	1040	156	676	208	3·3	Advanced
		5 days		46	860	69	464	327	1·4	Normal*
3	3	0 hours	Untreated	477	1170	80	950	140	6·8	Advanced
		21 „	18 hr. after starting insulin	370	1070	118	728	224	3·3	Advanced
4	12	0 days	In diabetic coma	1570	1005	151	653	201	3·2	Advanced
		129 „	Peripheral neuritis and gangrene	200	637	32	369	236	1·6	Normal
Normal range (Salt and Wolff 1957)					466–860	0–105	302–576	152–283	1·6–3·0	Normal

* Denotes leading edge of beta-lipoprotein band advanced toward the anode.

abnormality was present before the vascular complications, and that later, when the blood-sugar level was 200 mg. per 100 ml., the lipoprotein pattern was normal despite the persistence of the vascular complications.

Table II shows that in these patients the beta-lipoprotein levels closely followed the blood-sugar levels, but that no corresponding changes took place in the levels of the omega and alpha fractions of lipoproteins. In all uncontrolled patients the beta-lipoprotein peak occupied an advanced electrophoretic position, and in some instances that peak appeared to be heterogeneous with a subfraction (designated *) lying ahead of the main peak. Moreover case 4, when in diabetic coma, showed a fraction of alpha-lipoprotein in a position ahead of albumin—a feature already reported by Salt and Wolff (1957).

Discussion

Classical investigations into the disorder of lipid metabolism in diabetes mellitus (summarised by Peters and Van Slyke 1946) led to the view that, in severe cases with a tendency to ketosis and acidosis, there was a general increase of all the blood-lipids. The degree of lipæmia was thought to depend not on the severity of the diabetes but rather on the success of insulin therapy in controlling the disorder of carbohydrate metabolism. In diabetic patients who utilise sufficient carbohydrate the serum-lipid levels and patterns were regarded as substantially normal.

Our findings in children, which now include observations of the serum-lipoprotein fractions, are in the main in agreement with the classical view. The three initially untreated patients, in none of whom ketosis was severe, and the one who developed diabetic coma all presented with high levels of total lipids and beta fractions in the serum. Under insulin treatment, as the blood-sugar level fell, those high serum-lipid levels reverted either to normal or, in case 3 observed for a short time only, toward normal.

Among the diabetes-clinic patients the mean values in both subgroups all lay within normal limits, except the mean phospholipid levels. Attention thus became focused on certain statistically significant differences between the means in the two subgroups. In subgroup B the levels of cholesterol, esterified fatty acid, and beta-lipoprotein lipid in the serum were significantly higher than those in subgroup A. It seemed reasonable to infer that the increased lipid of the beta-lipoprotein complex was mainly cholesteryl ester, with some phospholipid, perhaps, in certain cases. However, we emphasise that the principal finding in this study is the higher level of beta-lipoprotein in the serum of diabetic children with higher blood-sugar levels, irrespective of the exact nature of the lipid constituents of the beta-lipoprotein complex.

Bowen (1951) examined by Tiselius electrophoresis the beta-globulin-bound lipid in the sera of healthy people and diabetic patients; he correlated the total cholesterol in the serum with extractable beta-lipid and found no significant difference between the correlation established for the healthy people and that for the well-controlled diabetic patients.

Baker et al. (1955), who studied the serum-lipoproteins by paper electrophoresis in diabetes-clinic patients, mainly adults, and in controls, found the beta/alpha ratio significantly higher in the diabetic patients, especially when the diabetes was accompanied by clinical evidence of atheroma. Such high beta/alpha ratios have been described in non-diabetic atherosclerotic patients by Rosenberg et al. (1954).

Keiding et al. (1952), Barach and Lowy (1952), and Tuller et al. (1954) investigated the levels of cholesterol and of ultracentrifugally separated lipoproteins in the serum of diabetic patients with vascular complications. Although the relationships are not fully understood, there appear to be definite links between disorders of serum-lipids and the development of arterial disease in diabetes. In the present case 4 the lipid abnormality preceded the vascular complications, but was reversible despite persistence of those complications.

Harris et al. (1953) showed that the hyperlipæmia of diabetic acidosis involves all fractions of the serum-lipids, especially the triglyceride fat.

Waagstein (1955) correlated the amounts of total lipids in the serum with blood-sugar levels in diabetic patients.

Hirsch et al. (1953) correlated the increased amounts of esterified fatty acids in the serum with high blood-sugar levels in diabetics.

Our results suggest that, during the course of diabetic illness, there may be repeated intermittent rises of level of beta-lipoprotein lipid in the serum whenever the blood-sugar level is raised through inadequacy of insulin action. The main ground for this speculation lies in the finding of statistically higher levels of beta-lipoprotein lipid in the serum of patients who, though free from ketosis and acidosis, had higher blood-sugar levels at the time of examination.

Further support is seen in the speed with which the levels of the beta-lipoprotein fraction returned to normal in the previously untreated patients as the blood-sugar levels fell under treatment with insulin, even when initial ketosis had not been severe. How rapidly the level of beta-lipoprotein in the serum follows the blood-sugar level in the controlled diabetic cannot be deduced from the studies reported here

In considering the several factors which may determine the rise of the serum-beta-lipoprotein level, hæmoconcentration (Harris et al 1953) may be set aside as regards our group of clinic patients Similarly, normal alimentary absorption, which is known to lead to an intermittent increase in the omega (chylomicron) fraction in the serum, without significantly affecting the beta and alpha fractions, can be disregarded, provided that utilisation is unimpaired

The important mechanisms of mobilisation of lipid from the adipose-tissue stores must next be considered It is known that, when carbohydrate is unavailable, lipid is mobilised to meet energy requirements, in diabetes a raised blood-sugar presumably indicates unavailability of glucose The mobilised lipid may be non-esterified fatty acid bound to albumin (Dole 1956, Gordon and Cherkes 1956, R S Gordon 1957) or very-low-density lipoproteins including chylomicrons (Havel 1957)

Although in part the mobilised material may consist initially of triglyceride fat, Salt and Wolff (1957) have observed that, in malnutritional states, the beta-lipoprotein level in the serum was raised and, in addition, the beta-lipoprotein took up an advanced electrophoretic position—a feature again noted in all our diabetic patients who were either untreated or out of control

It seems that lipolysis of mobilised lipid liberates fatty acid, and this may attach itself to beta-lipoprotein (besides albumin) and in extreme cases even to alpha-lipoprotein, thus causing increased electrophoretic mobilities of those lipoprotein fractions

Lastly, in considering raised levels of the serum lipoproteins, it is uncertain whether, or to what extent, there may be impairment of utilisation If this is a factor, both the quantity and the lability of absorbed alimentary lipid deserve consideration

The outstanding problem of childhood diabetes is the prevention of arterial complications Possibly this could be achieved through control of the blood-lipid levels, especially that of the beta-lipoprotein fraction To this end our findings confirm the desirability of maintaining a strict control of blood-sugar levels because this in turn would limit the degree of intermittent or persistent hyperlipæmia However, the difficulties of maintaining strict control, particularly in children, are considerable, and some additional and more direct attack on the hyperlipæmia therefore seems desirable

The feeding of fats containing a high proportion of unsaturated fatty acids has been widely advocated recently as a means of lowering blood-lipid levels in the hope of preventing atherosclerosis Already Kinsell et al (1954) and E S Gordon (1957) have fed such diets to diabetic patients and were successful in lowering the levels of certain lipid constituents in the blood A similar prolonged dietary trial in diabetic children before the onset of arterial disease should yield important evidence about whether or not a blood-lipid abnormality is a cause of the arterial complications in diabetes By inference it might even throw further light on the ætiology of atheroma in non-diabetic persons So far we have fed to one diabetic patient an emulsion of unsaturated triglyceride with resultant lowering of her serum-lipid level Further experiments along these lines are planned

Summary

Specimens of blood from 35 children, all under good or fair diabetic control, were analysed for the levels of sugar in the blood and for the levels of total lipid, lipoprotein-lipid in three electrophoretic fractions, cholesterol, esterified fatty acid, and phospholipid in the serum

The mean levels of beta-lipoprotein lipid, cholesterol, and esterified fatty acid in the serum were significantly higher in the children with blood-sugar levels above 200 mg per 100 ml than in those with levels below 200 mg per 100 ml A progressive rise of beta-lipoprotein level in the serum was observed with a rising blood-sugar level

In three hitherto untreated patients with only moderate or slight ketosis the initial levels of serum-lipid were high, the rise being largely due to the beta-lipoprotein fraction Under treatment with insulin, as the blood-sugar level fell the level of beta-lipoprotein in the serum also fell, in 2 cases it reverted to normal within one or a few days

One girl, a long-known diabetic, was found to have a very high level of total lipid and beta-fraction in her serum when admitted in coma Her recovery was complicated by gangrene and peripheral neuritis Four months after the coma, when the complications were still present, her serum-lipoprotein pattern was within the normal limits when the blood-sugar level was near normal In this case the serum-lipid abnormality preceded the development of arterial disease but remained reversible despite the persistence of complications

The results support a hypothesis that hyper-beta-lipoproteinæmia develops whenever insufficient carbohydrate is available for metabolic needs The high levels of beta-lipoprotein and cholesterol in the serum resemble those known to precede the development of atheroma in non-diabetic persons Although the increased amount of beta-lipoprotein has not been proved to cause the early development of arterial complications in juvenile diabetics, the facts strongly suggest the desirability of maintaining normal serum-lipid patterns

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INFLUENCE OF POSITION AND ACTIVITY ON THE SECRETION OF ALDOSTERONE*

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WHEREAS the diurnal rhythm in the urinary excretion of corticosteroids is well established, comparatively little is known about the day-and-night cycle of aldosterone Most workers have detected a diurnal pattern in ambulant normal persons On the other hand, Garrod, Simpson, and Tait (1957) did not find one in normal subjects who were recumbent, and this strongly suggested that the day-and-night difference in excretion of aldosterone depends solely on the position and activity of the person concerned To ascertain whether this is so, we made a series of observations on subjects who kept changing their position and activity

Methods

The subjects studied were healthy persons and a hypophyseal dwarf aged 19 All were maintained on a constant diet containing relatively little sodium On two occasions the patient with pituitary insufficiency was given prednisone by mouth every six hours

Urine was collected every twelve hours starting from 7 A.M and analysed for sodium and potassium in a flame photometer Creatinine was determined by the method of Folin (Peters 1942) and chloride by that of Sanz and Brechbuhler (1955) The urinary 17-hydroxycorticosteroids were determined by a modification of Reddy's method Hertoghe et al 1955) in the normal subjects and by the method of Norymberski and Stubbs (1954) in the hypophyseal dwarf Aldosterone was analysed chromatographically after acidification of the urine at pH 1 for twenty-four hours (method *d* of Neher and Wettstein 1955)

Results

Fig 1 shows the findings in a woman of 32 She ate three meals a day (at the same hours every day) containing less than 12 mEq of sodium In the first experiment NaCl 1 g (17 mEq) was added to each meal, whereas in the second experiment she ate the 51 mEq of salt during the night She maintained her normal activity, working regular hours, and always went to bed between 10 and 11 o'clock at night Despite this variation in the salt intake, there was in both experiments a clearcut regular day-and-night difference in the urinary aldosterone excretion The urinary output of sodium, however, was not greater by day than at night No correlation between the urinary excretion of aldosterone and that of sodium was found Potassium, 17-hydroxycorticosteroids, and water were always excreted in greater quantities by day than at night

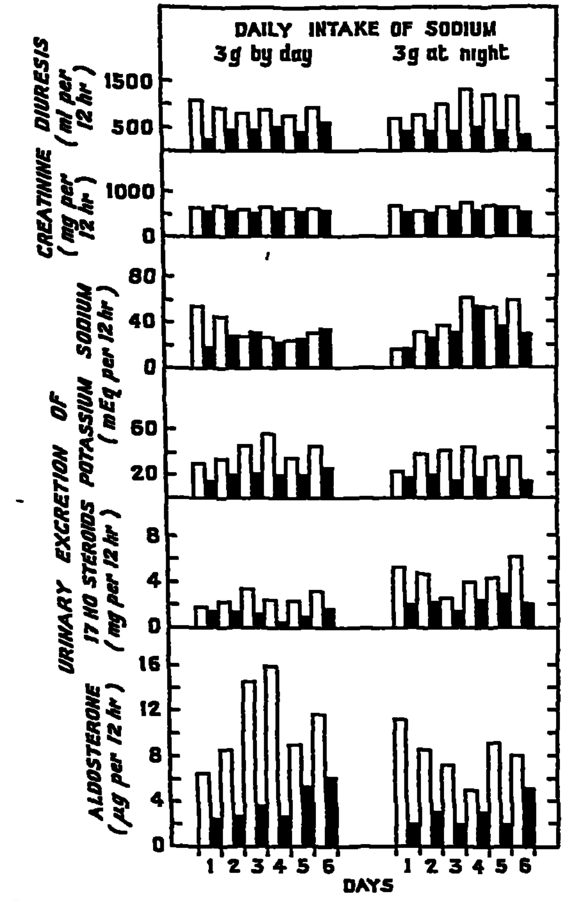

Fig 1—Influence of sodium intake on daily pattern of urinary excretion of aldosterone in a healthy woman leading a normal life Whether salt is taken by day or at night, urinary excretion of aldosterone, 17-hydroxycorticosteroids, and potassium is greater by day than at night. Urinary excretion of sodium has no definite day-and-night rhythm and no correlation with excretion of aldosterone

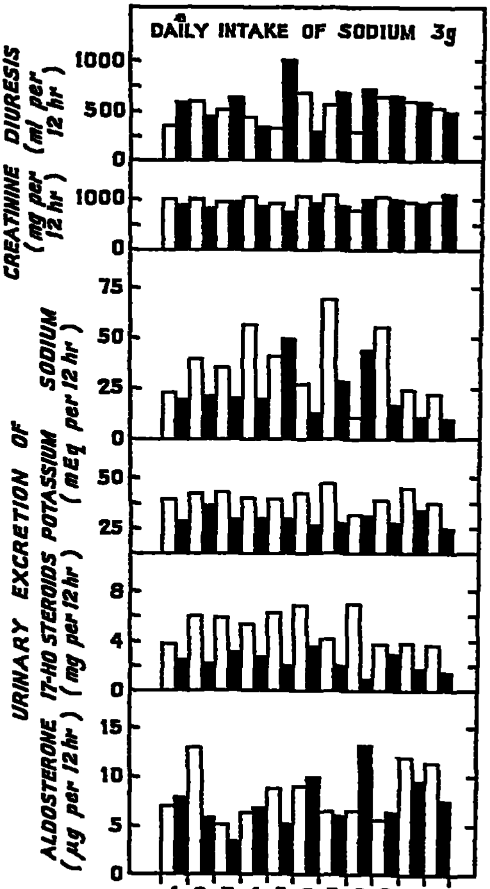

Fig 2—Diurnal and nocturnal urinary excretion of aldosterone in a healthy man with very irregular working hours, night and day Note absence of regular day-and-night pattern of excretion of aldosterone Contrast fig 1

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Fig 2 illustrates a similar study A man, aged 35, took a constant diet containing 3 g (50 mEq) of sodium daily, but he ate his meals at different hours of the day and night He was working irregular hours during the whole experiment, and his sleep was often interrupted On several occasions he was up and working a good part of the night In these circumstances there was no day-and-night difference in the excretion of aldosterone The output of urine and the excretion of creatinine were also less regular than in the previous study However, this time more sodium was excreted by day than at night The daily pattern of excretion of potassium and 17-hydroxycorticosteroids was identical with that found in the previous study

Fig 3 shows the results of a metabolic study of a healthy woman, aged 33, who intentionally changed position and activity during the day, whereas at night she was always horizontal in bed and inactive On the first, fifth, sixth, seventh, and ninth days she was up and ambulant, carrying on her usual activities On the second, third, fourth, and eighth days she lay flat and inactive in bed day and night The increased excretion of aldosterone during the day was clearly seen whenever she was up and working during the daytime As soon as she lay flat for twenty-four hours, the rhythm was interrupted and sometimes even reversed, with a larger excretion at night The overall excretion of aldosterone was greater when she was ambulant than when she was lying flat and inactive in bed Similar changes related to position and activity were found in the excretion of sodium While the woman was ambulant she actively retained sodium (89 and 8 mEq) and there was no difference in excretion between day and night As soon as she lay flat throughout the twenty-four hours, not only was sodium excreted (49 and 40 mEq) but also a daily pattern became manifest, with increased excretion during the day During this same period, for the first time, the ratio of aldosterone to sodium in the urine was inverted The excretion of chloride and the output of water had practically the same pattern as that of sodium, whereas potassium was excreted mainly by day In contrast to the aldosterone excretion pattern, the urinary 17-hydroxycorticosteroids were, throughout the study consistently higher during the day than at night, despite changes in position and activity

Fig 4 shows the findings in the male hypophyseal dwarf He was ambulant from 7 A M to 10 P M The rest of the time he slept flat in bed His urine was collected separately for those periods, and, since the periods were unequal, the results had to be expressed per hour During the last five days of the experiment the patient was given prednisone Despite his upright position and his activity there was no difference in urinary excretion of aldosterone between the day and the night when glucocorticoids (in his case prednisone) were withheld, but the increase in excretion of sodium by day was striking and apparently independent of the aldosterone excretion The night diuresis was also conspicuous and disappeared under treatment with prednisone The excretion of

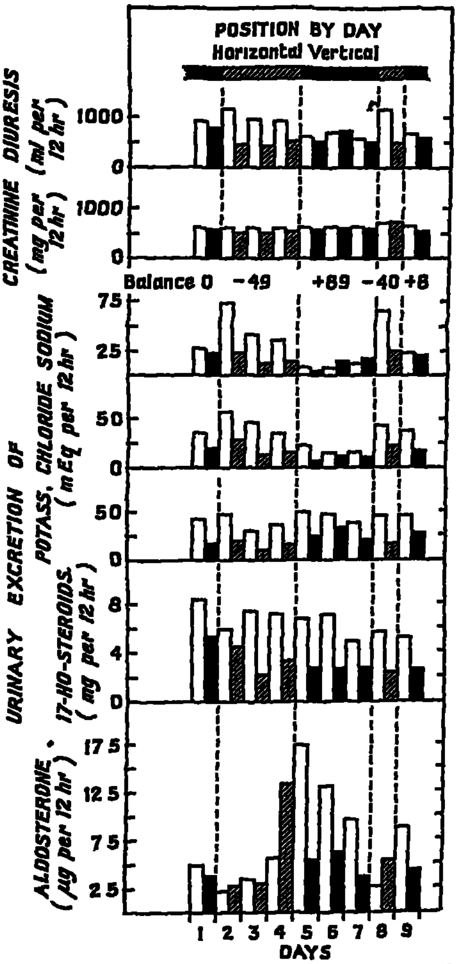

Fig 3—Influence of position on daily rhythm of urinary excretion of aldosterone in a woman, aged 33, who was always flat in bed and inactive at night but varied her position and activity by day Note discrepancy between day-and-night patterns of urinary excretion of aldosterone and 17-hydroxycorticosteroids, excellent correlation between those of aldosterone and sodium when the woman lay flat, and difference in sodium balance according to position

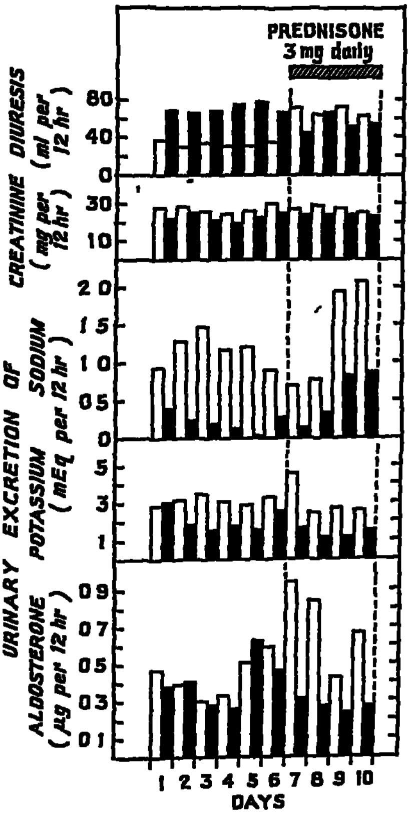

Fig 4

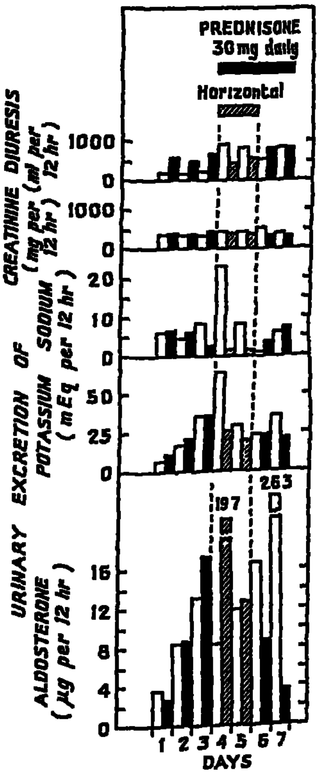

Fig 5

Fig 4—Daily urinary excretion of aldosterone in a youth, aged 19, with pituitary insufficiency Note absence of regular day-and-night pattern of aldosterone except under treatment with prednisone Sodium excretion, on the other hand, is consistently higher during the day Diuresis at night.

Fig 5—Same patient Influence of prednisone on urinary excretion of aldosterone in relation to position Note increased excretion of aldosterone by day when he was up and active, and important changes in diuresis and excretion of sodium, potassium, and aldosterone under treatment with prednisone and on changing position

potassium by day was again increased and hardly influenced by the administration of prednisone Despite the pituitary insufficiency, the excretion of 17-hydroxycorticosteroids still kept its daily pattern, with slightly increased excretion during the day (Not shown on the figure)

In a second experiment the same hypophyseal dwarf was again given prednisone, but this time while lying flat in bed for forty-eight hours (fig 5) The two experiments show that, when this patient was having prednisone, his urinary excretion of aldosterone increased in the daytime if he was ambulant and active but not if he was recumbent That is to say, the glucocorticoids (prednisone) per se did not alter the secretion of aldosterone their action seemed to be permissive Once again the excretion of sodium was not related to that of aldosterone, except to some extent when the patient was recumbent The output of urine was affected by the prednisone, and the excretion of potassium was very irregular

Discussion

These data, as well as those published elsewhere (Muller et al 1957), demonstrate unequivocally that position and activity influence the urinary excretion of aldosterone, whereas taking small amounts of salt at night instead of by day has no such influence On the basis of our earlier findings and those of other workers the increased urinary excretion of aldosterone can be taken, in the circumstances of the experiments, as reflecting increased secretion of aldosterone by the adrenal glands

Bartter (1957) has shown that a decrease in blood-volume stimulates the secretion of aldosterone Since (as has long been known) standing contracts the "effective blood-volume", it is very likely that the increase in urinary excretion of aldosterone really reflects a homœostatic mechanism set off by a decreased effective blood-volume due to the effect of position and exercise on the circulating blood-volume As Peters (1948) suggested, this mechanism may operate also in hæmorrhage and in congestive heart-failure

The retention and elimination of sodium shown at different periods in fig 3 certainly coincide, respectively, with increased and with decreased secretion of aldosterone It therefore seems that the increased retention of sodium on standing and exercise is caused by (among other factors) an increased secretion of aldosterone, which in turn is caused by contraction of the effective blood-volume In a similar way rest in bed increases the excretion of sodium by reducing the secretion of aldosterone

On the other hand, our results show, in the ambulant person, no correlation between the day-and-night cycles of sodium and of aldosterone They are therefore consistent with the view that alterations in the effective blood-volume on standing and exercise not only influence the secretion of aldosterone but also initiate acute renal adjustments in sodium excretion (Epstein et al 1951) These renal mechanisms seem to be independent of aldosterone, which explains their presence in Addison's disease The fact that the patient with pituitary insufficiency showed a constant difference between his diurnal and his nocturnal excretion of sodium, whether or not there was any such a difference in his excretion of aldosterone (fig 4), is another example of this dissociation between the sodium and aldosterone cycles In the recumbent subjects, however, the ratio between sodium and aldosterone in the urine tended to be inverted

The absence of a day-and-night difference in the excretion of aldosterone by the ambulant active patient with pituitary insufficiency is difficult to explain, so is the effect of prednisone in re-establishing this difference The fact that under treatment with prednisone this rhythm appears only if the patient is ambulant is another example illustrating the permissive rôle of the glucocorticoids Standing erect, by increasing the capillary filtration and the pooling of blood in the limbs, decreases both the effective and the total blood-volumes Possibly cortisone and prednisone influence this pooling of blood by increasing capillary permeability, whereby the effective blood-volume decreases, and the secretion of aldosterone is consequently stimulated

Summary

The difference between diurnal and nocturnal excretion of aldosterone in the urine was studied in three healthy people and one patient with pituitary insufficiency

The findings unequivocally demonstrate the influence of position and activity on the daily pattern of aldosterone excretion A small change in the diurnal and nocturnal intake of sodium chloride has no influence on this pattern The greater excretion of aldosterone by day seems to be the result of the erect position and activity A contraction of the effective blood-volume, as a result of standing and exercise, is postulated as the physiological stimulus of the aldosterone secretion However, the changes in sodium excretion due to position and exercise are mediated not only by the secretion of aldosterone but also by adjustments in renal mechanisms

In the patient with pituitary insufficiency the excretion of aldosterone was not greater by day than at night, despite ambulation and activity Treatment with prednisone re-established the greater excretion of aldosterone by day than at night, provided the patient was up and active, but not when he was lying flat

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TREATMENT OF SEVERE TETANUS BY CURARISATION AND INTERMITTENT POSITIVE-PRESSURE RESPIRATION

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Despite all treatment, the case-mortality of generalised tetanus is still high The physician has often been faced with the dilemma of a patient who may die either of cerebral anoxia due to tetanic spasms, or of respiratory paralysis (with aspiration of secretions) caused by increasing the dosage of sedative and relaxant drugs

Drawing on their extensive experience of bulbar poliomyelitis, Lassen, Ibsen, and their coworkers (1953, 1954,

1956) realised that the problem of respiratory paralysis can be solved by introducing, through a tracheostomy, a cuffed tube, through which artificial respiration may be applied They treated their tetanus patients by long-continued anæsthesia (N_2O and O_2), sometimes combined with administration of tubocurarine chloride A case treated successfully on these lines was reported by Shackleton (1954), who administered N_2O and O_2 with suxamethonium The use of full curarisation and intermittent positive-pressure respiration (I P P R) in tetanus has been reported by Honey et al (1954), Mollaret et al (1955), and Crampton Smith et al (1956)

We have treated two patients successfully by methods evolved by the Oxford workers, and we acknowledge with gratitude the assistance which we have received from Dr Ritchie Russell, Dr J M K Spalding, and, in particular, Dr Crampton Smith, whom we consulted frequently

Case-reports

THE FIRST CASE

A girl, aged 6, fell and sustained a tiny puncture wound on her knee on April 20, 1957 Seven days later tetanus came on rapidly, and four hours later she was admitted to hospital with severe spasms

Initial treatment After a preliminary test dose, antitetanic serum 100,000 units was given in the first twenty-four hours Further doses of 50,000 units each were given on the fourth, eighth, and twelfth days preceded by promethazine hydrochloride by mouth 25 mg there was no adverse reaction Penicillin was given for the first ten days, then withheld, and then given again from the twelfth day for twenty-one days following serious deterioration in the patient's general condition

Because paraldehyde and barbiturates did not control her spasms, mephenesin was added on the second day, 250 mg being given every half-hour by stomach-tube In spite of this the spasms became more frequent and more severe Her temperature rose steadily despite tepid sponging, ice packs, and the use of a fan, and reached 107°F forty-eight hours after the start of treatment

Artificial respiration In view of this deterioration, and in particular because of our inability to control her temperature, it was decided to give tubocurarine and maintain artificial respiration with a Radcliffe intermittent positive-pressure respirator

The child was anæsthetised by one of us (K J P) with nitrous oxide and oxygen, complete relaxation being obtained with tubocurarine After a cuffed endotracheal tube had been introduced, manual respiration was applied with a bag Tracheotomy was then performed by Mr Philip Scott, after which a short cuffed endotracheal tube was introduced and connected to a Radcliffe respirator Administration of nitrous oxide was discontinued, but oxygen 1 litre per minute was given with the inspired air The respirator was adjusted to give a minute volume of 4–5 litres

The following routine was then adopted

(1) Tubocurarine 10–15 mg was given intramuscularly with hyaluronidase, except when intravenous fluids were being given, when the tubocurarine was added with them The need of a further dose of tubocurarine was indicated by the appearance of muscular twitchings, which were regarded as modified tetanic spasms, and by any decrease in the respiratory minute volume which could not be accounted for by obstruction of the airway The daily requirement of tubocurarine varied between 95 and 250 mg (average 160 mg)

(2) Percussion and postural drainage were applied four-hourly during the day by the physiotherapist, who often gave additional treatment during the night

(3) The trachea and bronchi were cleared of secretions by suction through a soft rubber catheter each time the patient was turned, or more frequently if required Bronchoscopy was required on only two occasions Pharyngeal secretions were sucked out, and the cuff of the endotracheal tube deflated for two or three minutes every two hours

(4) The respiratory minute volume was measured half-hourly and any decrease remedied by suction, with further tubocurarine, or by adjustment of the respirator

(5) Temperature and pulse were recorded half-hourly, and a rise was found to be a useful indication of segmental or lobar pulmonary collapse

(6) The stomach-tube was aspirated hourly, and feeds of a fortified milk mixture* were given to supply the patient's estimated requirements of 1600 calories and 1500 ml of fluid daily Vitamins were also given routinely through the tube A transient increase in the gastric aspirations twenty-four hours after curarisation made it necessary to give intravenous feeding for twelve hours, after which normal gastric function returned and tube feeding was therefore resumed

Progress

On the fourth day Mr C C Jeffery excised the wound on the knee, removing a small piece of woody stem from a golden-rod plant, surrounded by a pocket of pus, from which *Clostridium tetani* was later isolated The wound was cleaned with hydrogen peroxide and sutured

On the eleventh day a severe episode of lobar collapse with cyanosis was followed by a rapid rise in temperature and pulse-rate, even after re-expansion of the lung had been obtained by bronchoscopy Four hours later, severe peripheral circulatory failure developed with unrecordable blood-pressure An intravenous infusion of noradrenaline was started immediately The amount of noradrenaline required to raise the blood-pressure to normal levels was so great that 16 mg had to be added to each 500 ml of 5% dextrose By this means the systolic blood-pressure was restored to 110 mm Hg after five hours After remaining critically ill for twenty-four hours the patient gradually needed less noradrenaline until, after forty hours, it was withdrawn completely

Chloramphenicol treatment of a superficial infection of the tracheostomy was begun on the day on which she developed peripheral circulatory failure, and eighteen hours later penicillin therapy was restarted and antitetanic serum 50,000 units was given The patient's temperature and pulse-rate then fell rapidly, reaching their previous levels after twenty-four hours

Her requirements of tubocurarine remained fairly constant for fifteen days, until, on the evening of May 15, the signs indicating the need for a further injection did not appear, and no tubocurarine was given Twelve hours after her last dose of tubocurarine the patient was taken off the respirator, having had I P P R for sixteen days Radiography showed that her chest was clear and her spine had no collapsed vertebra

THE SECOND CASE

A girl, aged 10, fell off a seesaw on June 23, 1957, sustaining a compound fracture of her right radius and ulna She was admitted to a local hospital, where the wound was cleaned and excised and the fracture reduced and put into plaster She was not given antitetanic serum Five days after her injury she developed tetanus, and was transferred to the Royal Devon and Exeter Hospital, accompanied in the ambulance by a consultant anæsthetist equipped with apparatus for intubation if required

Initial Treatment

After a preliminary test dose, antitetanic serum 200,000 units was given on the first day, and further injections of 100,000 units each were given on the second, third, fourth, and sixth days

The compound-fracture wound was opened up widely by Mr Jeffery, and *Cl tetani* was subsequently cultured from it Penicillin was given throughout the first three weeks in hospital

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* Fortified Milk Mixture 2 pints milk (1136 ml), 2 oz glucose (56 g), 2 oz 'Casilan (56 g), 2 eggs, 1 teaspoon 'Marmite , ½ teaspoon salt. Calorie value 1364

Mephenesin 200 mg half-hourly and quinalbarbitone gr $1^1/_2$ six-hourly were given by stomach-tube and paraldehyde 4 drachms by the same route as required to control the spasms (usually every three or four hours). Although for three days the spasms were fairly well controlled, the amount of paraldehyde required rendered the child deeply unconscious Although physiotherapy and postural drainage were applied four-hourly, on the fourth day of her illness her cough reflex became so diminished that she had a severe episode of bronchial obstruction with profound cyanosis A large amount of inspissated mucus was found in her mouth and pharynx Bronchoscopy was done immediately (K J P), and a plug of mucus was removed from the right main bronchus

Artificial Respiration

In view of these dangerous respiratory complications, treatment with tubocurarine and I P P R was instituted without delay Mr Raymond Hinde kindly carried out the tracheotomy

The general management was then similar to that in case 1 The amount of tubocurarine needed was 380–500 mg (average 440 mg) daily, and feeds of the fortified milk mixture were given to provide 2000 calories and 2 litres of fluid daily The respiratory minute volume was maintained at 6 litres per minute Seven hours after treatment with tubocurarine had been started, tube feeding had to be discontinued because large quantities of fluids were being aspirated from the stomach After thirty hours, during which time fluids were given intravenously, tube feeding was successfully resumed Transient collapse of her right upper lobe occurred on the third day of I P P R, but in general the chest remained remarkably clear

The child's need of tubocurarine remained fairly constant until the thirteenth day, when the drug was withheld without the development of tetanic spasms On July 15, after fourteen days' I P P R, she was finally taken off the respirator Radiography showed some vertebral compression of the 4th, 5th, and 6th dorsal vertebræ In all other respects her recovery was complete

DISCUSSION

Curarisation and I P.P R

For these two patients treatment with tubocurarine and I P P R was started only after large doses of hypnotic drugs and mephenesin had failed to control the spasms Indeed it must be admitted that our second patient was allowed to reach a point at which the laryngeal reflexes were dangerously depressed by sedation In the light of our experience with these two patients it now seems to us that all cases of tetanus in which the spasms cannot be controlled by moderate sedation and mephenesin should be treated by complete paralysis and I P P R

A further indication for the administration of tubocurarine in our first patient was our inability to control her extreme pyrexia Vigorous surface-cooling produced only chilling of the skin and violent shivering It was not until this shivering had been overcome by complete paralysis that the temperature could be lowered It did not seem advisable or necessary to enhance this treatment with a lytic cocktail as advocated by Rossi et al (1954)

After initial intravenous injection of tubocurarine, satisfactory results were obtained with intramuscular injection of the drug, usually with hyaluronidase Relaxation was evident in five minutes

Sedatives and hypnotic drugs were used sparingly in the later stages of treatment in case 1 and scarcely at all in case 2 Ten days after the cessation of treatment neither of these children, both of whom are of at least average intelligence, could recall any detail of their period of artificial respiration In particular they have no recollection of any pain Possibly the respirator may have induced a slight degree of hyperventilation, which may partly explain some of the clouding of consciousness and subsequent amnesia

Artificial respiration was given along the lines described by Crampton Smith et al (1956), a standard Radcliffe respirator being used For the most part the patients breathed ordinary air to which oxygen 0 5–1 0 litre per minute was added There was no indication for the use of nitrous-oxide anæsthesia once the tracheostomy was completed, indeed the dangers of aplastic anæmia following long-continued administration of this gas (Lassen et al 1956) strongly contraindicated such a procedure

Movements of the eyes and tongue were often noticed when the patient was otherwise completely paralysed and gave no indication of the need of more tubocurarine

Physiotherapy and Tracheobronchial Toilette

Pulmonary complications were fewer than was expected This appeared to be due largely to the postural drainage applied by an expert physiotherapist five times each twenty-four hours, and more often if required, and to the routine toilette of the tracheobronchial tree by at least half-hourly aspiration through a soft rubber catheter Undoubtedly the humidification of the inspired air (Marshall and Spalding 1953) and the fact that the foot of the bed was kept constantly raised were also important factors in this respect

The inevitable transient episodes of pulmonary collapse could be quickly detected by a rising pulse-rate, slight cyanosis, and a simultaneous decline in the respiratory minute volume unexplained by the need of more tubocurarine Re-expansion could readily be obtained by vigorous physiotherapy and aspiration Frequent chest radiography was of little value in view of the rapidity with which the chest condition altered

Specific Therapy

Antitetanic serum —Both patients were given large and often repeated intramuscular injections of antitetanic serum, each preceded by an oral anti-histamine drug No ill effects were detected, indeed the temperature and pulse-rate fell on several occasions a few hours after the injection

Reference must be made also to the dramatic deterioration in case 1 on the eleventh day of the illness

We have no doubt that she would have died at this time in peripheral circulatory failure if she had not responded to the noradrenaline infusion It is of interest that the penicillin given from the start of the illness had been stopped two days before this collapse, and no antitetanic serum had been given in the previous four days The child remained extremely ill with high fever (104 2°F) for eighteen hours until a further intramuscular injection of antitetanic serum 50,000 units was given Within four hours of this she rapidly improved, and shortly afterwards it became possible gradually to withdraw the noradrenaline infusion Though the possibility that this episode of profound toxæmia was due to *Staphylococcus pyogenes* septicæmia obtaining entry through the tracheostomy wound cannot be excluded, a true tetanus toxæmia, not relieved until more antitetanic serum was given, seems to us to be much more probable

Thus we cannot accept the view of various American authorities (Abel et al 1938, Dietrich 1940), who advise only a single injection of antitetanic serum, or of Spaeth (1940), who deprecates its use altogether Provided that a test dose produces no reaction and that each injection is preceded by an anti-histamine drug, the treatment of tetanus with large repeated intramuscular injections of serum is in no way superseded by the additional techniques here discussed, indeed it is still one of the sheet anchors of treatment Rapid desensitisation by multiple injections of increasing strength can be achieved if the initial test dose of serum gives a positive reaction

Antibiotics—Penicillin is clearly indicated as long as active signs of clinical tetanus persist Other antibiotics may be required to prevent respiratory complications

Excision of wound—When the wound was explored in both patients *Cl tetani* was isolated This fact re-emphasises the need to explore even the most trivial wound in every patient with tetanus

Fluid balance—It was possible for most of the time to give adequate fluids, electrolytes, vitamins, and a high-calorie diet by stomach-tube In both patients gastric function failed temporarily soon after the start of treatment with tubocurarine and I P P R Possibly cessation of normal diaphragmatic movement plays a part in this failure During this period large quantities of fluid had to be aspirated from the stomach, hence the electrolyte requirements had to be carefully watched and supplied

General Supervision

During the treatment of case 1 by I P P R a "shift" system was instituted by which a doctor was always present with the patient throughout the twenty-four hours, but during the treatment of case 2 by I P P R we relied instead on third-year student nurses, because we thought that the disruption of the work of a busy hospital which a shift system causes was unjustifiable These nurses gave all the routine treatment, including tubocurarine and tracheobronchial toilette, in a highly efficient manner A system of alarm bells was installed so that in an emergency medical help would be immediate, but this was never used

Active Immunisation

Finally, we emphasise that, in rural areas particularly, there is still a small but recurring morbidity and mortality from tetanus More widespread use of active immunisation in childhood in such areas is most strongly to be recommended

Summary

The detailed treatment of two children with severe tetanus by complete paralysis and intermittent positive-pressure respiration is described

These additional techniques in no way supersede the established forms of treatment—e g, large repeated intramuscular injections of antitetanic serum

Whatever recovery-rate may be achieved even in severe cases of tetanus, more widespread use of active immunisation in childhood, especially in rural areas, is strongly recommended

We wish to record our thanks to our colleagues who have been mentioned in the text, and also to Dr W J Walter, Dr G S Steele-Perkins, and Dr Butler, consultant anæsthetists, to Dr N S Alcock, consultant neurologist, and to Dr P C Gautier-Smith, resident medical officer, and to all the other members of the resident medical staff, all of whom were involved directly or indirectly in the care of these patients Our thanks are due also to Sister Ashby and the nurses, to the physiotherapists, and to Mr Berry, who maintained the apparatus

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PERCUTANEOUS INTUBATION OF THE FEMORAL VEIN FOR TRANSFUSION

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INTRAVENOUS transfusion is usually made through a suitable needle inserted into a vein of the arm or the leg When this method is unsuccessful or a prolonged transfusion contemplated, a vein may be exposed through a small incision and a cannula tied in Neither method is without disadvantages The use of a needle entails immobilisation of the limb, and thrombosis of the vein is a not uncommon sequel Further, when blood is given, the transfusion rarely runs for more than twenty-four hours Cannulation of the vein entails its ligation and ultimate obliteration Neither method can be used with safety for vesicants or strong dextrose solutions, and both may fail where profound shock is accompanied by intense constriction of the peripheral veins

The ease with which a small nylon catheter may be inserted into a vein in the arm (Verel 1954) suggested that a larger catheter might be of value for blood-transfusion Russell et al (1954) had used a polyethylene tube inserted into the femoral vein by cut-down in the management of anuria and found it remained patent for many days The femoral vein is easily punctured and had been used on several occasions for obtaining blood samples from severely shock subjects A technique was therefore devised for inserting a large catheter into the femoral vein through a suitable needle

Materials

Nylon tubing into which a standard blood-transfusion needle would fit was first obtained ('Portex' no 3 or 'Becton Dickinson' 0 65 in are suitable) Three sizes of stainless-steel tubes were then prepared

(1) A cannula 3 5 cm long fitting into the tubing easily but without leaks,

(2) A cannula 3 5 cm long fitting the tubing very tightly, and

(3) A needle through which the nylon tubing passed easily but not loosely (this was ground to a sharp bevel and fitted for convenience of handling with a Luer hub)

Method

The needles are dry-sterilised in individual glass tubes The nylon tubing is cut as needed and boiled in a bowl or autoclaved before use It should not be picked up with forceps when warm, because this may pinch it flat For most purposes a 20–25 cm length is used, one end is cut square and the other with a 45° bevel

A trolley is laid out with 3 sterile towels, 2 syringes of 5 ml capacity, several intradermal needles, a 5 cm 19-gauge needle, and ampoules of physiological saline solution, heparin, and 2% procaine solution A 5 ml syringe is first filled with physiological saline solution containing a drop or two of heparin and the small cannula is attached to it The square-cut end of the tubing is then threaded on to this, the cannula is filled with heparin-saline mixture, and the bevelled end is passed through the introducing needle to make sure that sterilisation has not affected the fit of the tubes (polyethylene tubing is unsuitable because it swells on boiling and tends to split when cannulæ are pushed into it) A second 5 ml syringe is then filled with 2% procaine, and a short intradermal needle is attached to it

The patient is then laid supine, with only the head raised on pillows (For orthopnœic patients the head of the bed is raised on blocks) The thigh on the side to be intubated is then abducted to about 45° to the trunk and everted so that it lies easily on the bed The pubic tubercule is then identified, and

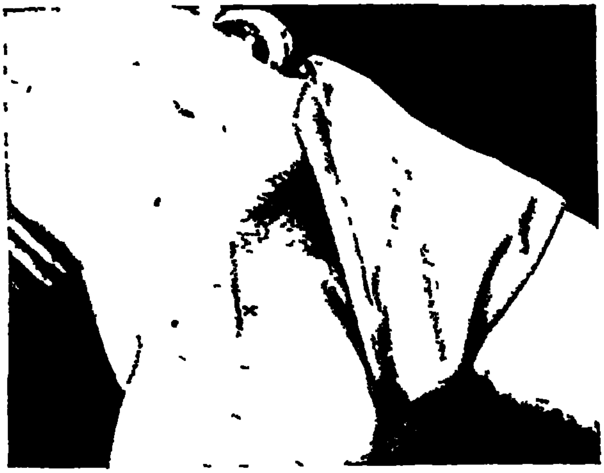

Fig. 1—Thigh positioned for intubation. Line of femoral artery marked with a skin pencil; cross shows approximate site for infiltration with local anæsthetic.

the course of maximal pulsation of the femoral artery is marked clearly on the skin from the point at which pulsation can be felt above Poupart's ligament to at least 12 cm. below it (fig. 1). Once this has been done, the patient's thigh is not moved until the transfusion is running.

A point is then selected 4–5 cm. below Poupart's ligament and 5–8 mm. medial to the line of maximal arterial pulsation. After the skin has been carefully cleaned, the skin and subepithelial tissues are infiltrated with about 2 ml. of local anæsthetic. The 5 cm. 19-gauge needle is then attached to the syringe and, through the same puncture, introduced at an angle of 45° to the skin, advancing upwards towards Poupart's ligament parallel to the artery but 5–8 mm. medial to it. Each time the needle-point encounters a fascial plane the advance is halted and the syringe held lightly to see if any transmitted pulsation indicates that the artery lies beyond the needle. If none is felt and aspiration yields no blood, 0.5 ml. of local anæsthetic is injected, and the needle is advanced to the next point of resistance until either the femoral vein is encountered or bony resistance is felt. If bone is encountered, the needle is carefully palpated to determine whether it has passed between the artery and vein or medial to the vein, and, after withdrawing the needle into the superficial tissues, a corrected direction is tried. Should the artery be entered by mistake, it is easily distinguished by the colour of the blood. Blood-pressure may be misleading because, if the patient is lying with the head of the bed raised, the pressure in the femoral vein is enough to force the plunger of the syringe out. Once the femoral vein has been identified, the angle and depth of the needle in relation to the line of the artery marked on the skin are carefully noted.

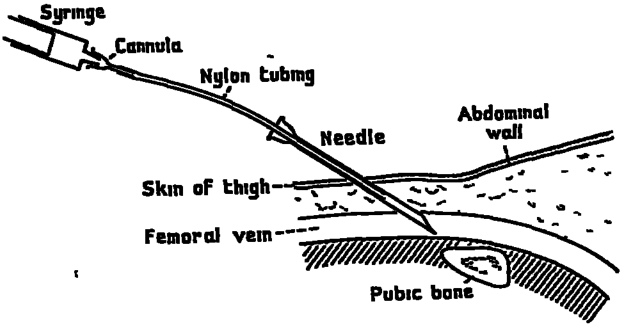

Fig. 2—Femoral vein pierced by introducing needle: point of needle lies within femoral vein, and nylon tubing is in needle and connected to syringe by easily fitting cannula.

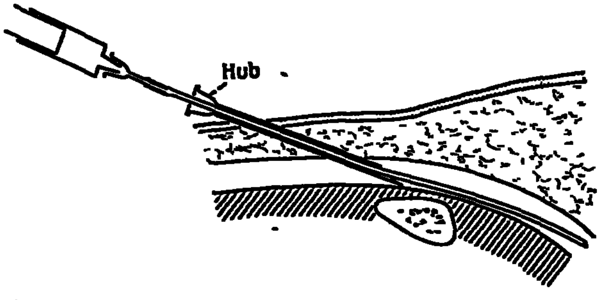

Fig. 3—Needle depressed until hub touches thigh, and tubing passed through needle until syringe and cannula are close to needle-hub.

Sterile towels are then applied so that only a small area round the site of the injection is exposed. An assistant prepares a transfusion set, attaching the large cannula to the nipple of the set. The catheter with attached syringe and introducing needle is now laid on the sterile towel and drawn back so that its tip lies within the introducing needle. The needle is then pushed through the skin at the site of the local infiltration, the needle being held in the line of the artery and almost parallel to the skin of the thigh because considerable force is needed to penetrate the dermis and, if this is attempted with the needle at 45°, all tissues down to the pubic bone may be suddenly transfixed. (Alternatively the needle may be introduced through a puncture made with a small tenotome.) The needle is then drawn back until only its tip is within the skin, and it is raised to 45°. The position of the artery is checked by palpation, and the needle is gently advanced until the first resistance is felt. If there is no transmitted pulsation and aspiration by the syringe on the end of the tube produces no blood, the needle is pushed on and the aspiration repeated. The sequence of advance, pause to check for pulsation, and then aspiration is repeated until venous blood is drawn into the tubing, indicating that the femoral vein has been entered (fig. 2). (Usually the vein wall causes moderate resistance, and the ease with which the needle can be advanced in the lumen of the vessel is recognisable.) The blood is then ejected from the tubing by

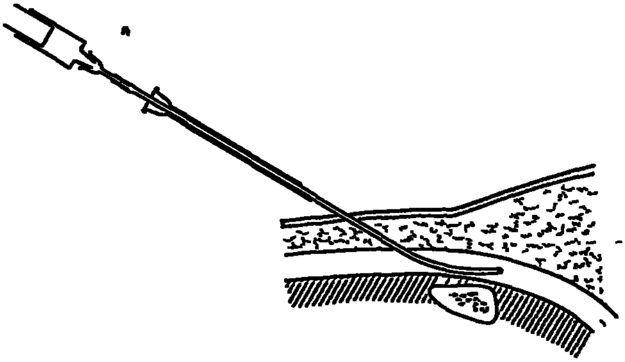

Fig. 4—Introducing needle withdrawn with syringe and cannula. Assistant now fixes tubing where it enters skin by firm pressure while cannula is withdrawn and needle removed.

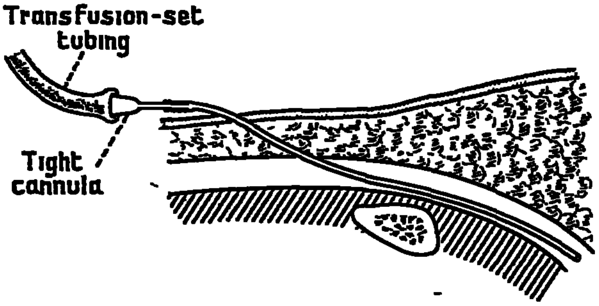

Fig. 5—Tightly fitting cannula connected to transfusion set is now inserted into nylon tubing, and transfusion is started. Nylon tubing is then pushed well up into vein, and cannula and transfusion-set tubing are taped to skin.

PATIENTS TRANSFUSED INTO FEMORAL VEIN

Case no	Duration of transfusion	Volume transfused	Nature of fluid	Diagnosis	Indication for use of tubing
1	3 days	7 pints	Blood	Hæmorrhage from œsophagus	Profound shock, no peripheral vein suitable
2	1 day	3 pints	Blood	Hæmolytic anæmia	No suitable vein remained
3	1 day	3 pints	Blood	Ulcerative colitis	Previous cut down, no suitable superficial vein
4	1 day	2 pints	Blood	Emphysema, peripheral circulatory failure	Profound shock, no peripheral vein suitable
5	6 days	20 pints	Electrolyte, glucose and packed cells	Anuria	Election
6	2 hr	1/2 pint	Saline solution and N_2 mustard	Hodgkin's disease	Previous thrombosis of forearm vein
	"	"	"		
	"	"	"		
	"	"	"		
	1 day	"	Saline solution, N_2 mustard, and blood 3 pints		
7	2 days	7 pints	Packed cells	Chronic gastrointestinal hæmorrhage, heart failure	Election
8	1 day	4 pints	50% glucose, electrolytes	Pulmonary tuberculosis, anuria following hæmorrhage	Election
9	8 hr	2 1/2 pints	Blood	Gastrointestinal hæmorrhage	Profound shock, no peripheral vein suitable
10	1/2 hr	100 ml	50% sucrose	Raised intracranial pressure	Poor peripheral veins
11	5 days	6 pints	Blood	Hæmatemesis	Election
		8 pints	Electrolytes	Pyloric stenosis	
12	12 hr	3 pints	Packed cells	Acute leukæmia	Election
13	12 hr	3 pints	Blood	Acute hæmorrhage	Profound shock
14	21 hr	2 pints	Blood	Postoperative transfusion	Election
		3 pints	Electrolytes		

injecting heparinised saline solution, the syringe being held so that any bubbles which may have entered are retained in the syringe

The tubing is now pushed gently forwards Sometimes the tube will pass easily up the femoral vein with the needle at 45° to the skin More usually, after advancing about 1 cm beyond the end of the needle, it sticks although aspiration reveals that it is still in the vein This arrest is probably due to the acute angle of entry. The tube is withdrawn a few mm and the needle-hub lowered to the level of the skin of the thigh, a single layer of sterile towel only separating the two In this position the tube is passed in until only 1 cm remains outside the introducing needle (fig 3)

The end of the tubing with the narrow cannula and the introducing needle are now gripped firmly, and the introducing needle is withdrawn until about 0 5 cm of the tubing is visible between the needle-tip and the skin (fig 4) An assistant then fixes this by firm pressure with a swab over the puncture The narrow cannula is now drawn out of the tubing and the introducing needle slipped off The tubing slides easily in and out of the skin puncture, so a careful watch at this stage must be kept to prevent the tubing from being completely pulled out with the needle During this manœuvre saline solution and then blood should flow freely from the catheter The large cannula is then connected and the transfusion started The nylon tubing may then be pushed into the vein (fig 5) The tubing of the transfusion set is taped to the skin in three places If blood still leaks from the site of entry, a collodion dressing is applied

At the end of the transfusion the catheter is removed and light pressure over the puncture is applied for one or two minutes. In all cases a nurse has been responsible for its removal

Note Two cannulæ are used because the large one is tight enough to dilate the nylon tubing slightly If this were used in the preliminary stages it would prevent the removal of the introducing needle at the end of the intubation

Results

Details of the first 18 occasions on which femoral-vein intubation was used are shown in the accompanying table Its use was originally restricted to patients in whom conventional methods were impossible, but it has proved so convenient that it is now preferred to both cut-down and simple transfusion with an intravenous needle in any patient in whom the transfusion is expected to run for more than twenty-four hours

The tubing has proved suitable for transfusing stored blood, packed cells, electrolyte and glucose solutions, and nitrogen mustard without mishap

The puncture in the femoral vein was identified in case 8, who died twenty-four hours after the transfusion was set up There was a clean hole in the intima without any surrounding thrombosis or any subcutaneous extravasation of blood

Three colleagues have used the method successfully on their own patients and prefer it to cutting down on a vein

Some difficulties have been encountered

In the first case in which the method was tried the catheter would not enter the vein, although the needle was apparently correctly placed. The patient was very obese, and the vein was punctured only when the introducing needle had entered up to the hub. A longer needle (9 cm) was made for use in such patients when it was realised that the acute angle of entry might cause the catheter to stick

In one patient the catheter slipped out of the vein during the removal of the introducing needle Careful fixing of the catheter by pressure where it enters the skin has prevented a recurrence of this mishap

In several instances during transfusion of blood the flow ceased On all of these occasions the tubing was patent, and the block was found in the transfusion set, except in one case where the transfusion stopped at another hospital and the site of the block was not identified

The longest transfusion in this series ran for six days The tubing may be used for much longer periods, however In one patient with anuria a similar transfusion was set up into an arm vein It was used for giving blood and solutions of dextrose and electrolytes for more than three weeks When the tubing was removed because it was no longer needed, there was no evidence of blockage or of venous thrombosis

7 patients who had previously been transfused by conventional methods were questioned by an independent observer after transfusion Five expressed a preference for the use of the femoral-vein intubation, one would express no preference, and case 2 had a strong dislike of the femoral-vein approach Since case 2 had been subjected elsewhere to twenty-five transfusions mostly by cut-down, no suitable vein remained Fortunately a remission in her hæmolytic anæmia made further transfusion unnecessary

The nurses preferred the use of the femoral vein because the patient retained the use of all four limbs, and all ordinary nursing care, including the use of the bedpan and blanket bathing, was possible, patients fed themselves and slept comfortably on their sides if they wished, no patient turned over on to the tubing in his sleep, because the firm attachment by sticking-plaster to the unshaven thigh woke them if they tried to do so The ease with which patients could be moved is well illustrated by 2 instances case 5 was transferred by ambulance for fifteen miles to another hospital, the transfusion being continued during the journey, and gastroscopy was performed on case 11 during transfusion

Summary

A technique for passing a nylon tube into the femoral vein through an intravenous needle is described The tubing has proved suitable for transfusing whole blood, packed cells, and solutions of electrolytes, glucose, 50% dextrose, and nitrogen mustards

No complications were encountered During transfusion the patients may move freely and may be transported by ambulance Gastroscopy was done on one patient during transfusion

The method is simple and provides a certain method of transfusion in severe shock, where venous spasm may render conventional methods ineffective It is now preferred to tying in a catheter and simple needle insertion in any patient in whom transfusion is expected to last more than twenty-four hours

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Verel, D (1954) *Clin Sci* 13, 51

RECURRENT FACIAL EMPHYSEMA

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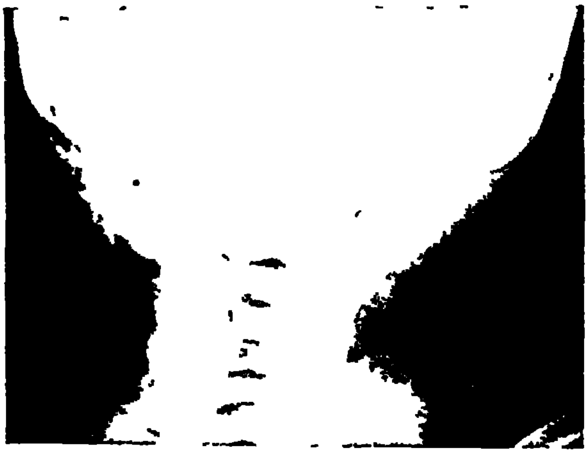
EMPHYSEMA of the subcutaneous tissues of the face and neck usually results from a traumatic or surgical opening in the wall of the mouth, œsophagus, or respiratory tract Commonly the air reaches the face by upward spread from mediastinal emphysema or from extensive collections of air in the chest wall Emphysema confined to the face and neck is relatively uncommon and is usually a complication of tracheotomy, bronchography by the cricothyroid route, dental extractions or operations (Brown 1949), or puncture of the antrum

Spontaneous mediastinal emphysema is rare (Matts 1957) and spontaneous emphysema of the face even rarer, but Jackson and Jackson (1936) wrote "subcutaneous emphysema occurs spontaneously in a few cases probably the result of rupture of the mucosa of the upper air and food passages"

A curious type of facial emphysema was described by Reading (1950) under the title of "autemphysesis" a German prisoner-of-war produced extensive emphysema of the face and neck by means of a small incision on the inner side of the left cheek The patient stated that this could be produced by a razor-blade or by nipping the cheek between the molars Air was then forced into the tissues of the neck by expiration with the mouth closed and nose pinched between finger and thumb

Similar cases were observed during the Middle East campaign, and a medical directive was sent out to warn medical officers to look out for these cases, which presented like mumps



Emphysema of subcutaneous tissues on right side of neck.

In the case described here we could not find any cause for the emphysema, and we publish the case partly because of its intrinsic interest and partly because we hope that others may be able to explain the recurring emphysema

Case-report

A girl began, at the age of $8^1/_2$ years, to have episodes of swelling of the face During the first attack she was thought to have mumps, but the recurrence of the swelling at intervals of about a fortnight excluded this diagnosis The swelling affected either side of the face but only once occurred simultaneously on both sides, and seldom lasted more than two or three days The swelling was greatest over the parotid region in the first attacks There was no pain, but the girl occasionally complained of discomfort in the ears and of "crackling in the gums" The significance of the crackling sensation was not appreciated until the correct diagnosis had been made The attacks always came on when she was upset at school, which she did not like Apart from this there was no indication of a possible cause of the swelling

On Aug 11, 1956, at the age of 9 years, she was referred to the pædiatric outpatient clinic at the Greenock Royal Infirmary At this time there was no swelling, and recurrent parotitis was provisionally diagnosed The regions of the parotid glands and ducts were radiographed, but no calculi were found In view of the absence of any residual enlargement of the parotids and in view of the painlessness of the swelling during the attacks, the diagnosis of recurrent parotitis did not seem wholly satisfactory, and it was suggested that she should be seen again when the swelling was present

She was seen at her home on Oct 2, 1956, when she had a swelling of the right side of her face, mainly in the parotid and infraorbital regions Pressure over the parotid gland did not cause pain Pressure on the inner side of the right cheek produced the crackling sensation of subcutaneous emphysema, and this was also present over the parotid gland and in the upper part of the neck A search was made for a lesion of the inner surface of the cheek, but none was found The gums and teeth were healthy, and there had been no recent dental extractions Radiography of the face, neck (see figure), and chest showed that the air was confined to the face and upper part of the neck on the right side There was no evidence of mediastinal emphysema or of pneumothorax

Later, when the swelling had subsided, the girl's teeth were examined, and Mr Ian Munro examined her ears, nose, and throat No abnormality was discovered, and radiography of her sinuses, maxillæ, and lower jaw was also quite normal

Discussion

The only clue to the cause of the emphysema was the association between emotional tension at school and the onset of swelling Since the child did not like her school, it seemed possible that she might be producing emphysema either deliberately or involuntarily while crying An accidental or deliberate puncture of the buccal mucosa with pen-nibs or pencil was denied, and the mother stated definitely that the swelling was not associated with crying Finally, an attempt to reproduce the emphysema by getting the girl to inflate a balloon did not cause any swelling of her face

During the following weeks she continued to have recurrent attacks of emphysema when she was upset at school In November, 1956, the Education Committee was asked to change her school When last seen in October, 1957, she had started at her new school and was quite happy Since her change of school she has had one brief episode of the emphysema due to coughing during an attack of influenza

There was thus no discoverable mechanical cause for the emphysema and no explanation for its association with emotional tension or for the appearance of the swelling on either side of the face

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Preliminary Communications

THE EFFECT OF HUMAN GROWTH HORMONE IN MAN

THE metabolic effect of growth hormone (GH) has been extensively studied in animals[1] In contrast, very little is known about the significance of GH in man GH purified from animal pituitaries has been used in metabolic studies in man, but the results obtained were either negative or inconclusive[2] It was shown later by Li and Papkoff[3] that GH purified from human pituitaries differs in chemical structural properties from the hormone purified from animal glands, and the behaviour of animal GH in man could be explained on this basis

TABLE I—RESULTS OF BIOLOGICAL ASSAY OF HUMAN GROWTH HORMONE

Preparation	Total dose (µg)	No of assay rats	Average tibia width* (µ)
84/57	20	5	190±5 3
84/57	80	5	226±6 7

* Mean ± standard error

In this communication we report preliminary results of metabolic studies on two volunteers given GH purified from human pituitaries Case 1 was a 35-year-old male, who had for many years suffered from rheumatoid arthritis, which had been clinically inactive for at least 8 years Case 2 was a male of 45, who had previously been treated for obesity His body-weight for the past three years had been 92 kg , and his height 185 cm

The metabolic studies involved standard procedures, using four-day collection periods for fæces and daily ones for urine

GH was given intramuscularly in a single daily dose of 10 mg , case 1 received injections for 12 and case 2 for 16 days

TABLE II—CUMULATIVE BALANCES OF NITROGEN, PHOSPHORUS, POTASSIUM, AND CALCIUM DURING ADMINISTRATION OF GROWTH HORMONE

—	Case 1	Case 2
Given GH for	12 days	16 days
Nitrogen balance (mg)	+40284	+40320
as protein in protoplasm (g)	252	252
as fat-free protoplasm (g)	1289	1290
Phosphorus balance (mg)		
calculated from nitrogen	+ 2686	+ 2688
actual balance	+ 2116	+ 2032
net balance (in relation to nitrogen)	− 70	− 656
Potassium balance (mEq)		
calculated from nitrogen	+ 109	+ 109
actual balance	+ 302	+ 186
net balance (in relation to nitrogen)	+ 193	+ 77
Calcium balance (mg)		
urine	− 888	− 720
fæces	+ 1572	− 1216
Total	+ 684	− 1936

Preparation of Growth Hormone

GH was purified from lyophilised human pituitaries, collected at necropsy, according to the chromatographic method of Li and Papkoff[3] The hormone content of the material was estimated qualitatively and quantitatively by zone electrophoresis on starch, and it was assayed biologically in hypophysectomised rats by the tibia test[4] (see table I).

When the GH preparation was submitted to zone electrophoresis on starch in a veronal buffer (0 01 M hydrogen veronal, 0 04 M sodium veronal, and 0 06 M NaCl) of pH 8 3 it migrated as a single protein No material remained stationary at the origin The GH preparation was easily dissolved in saline after adjusting the pH to around 7 0

RESULTS

Protein metabolism—The cumulative balances of nitrogen, phosphorus, and potassium during the treatment period are shown in table II In both patients a positive balance was obtained for all three elements The nitrogen retained in both corresponded to about 1 3 kg of fat-free protoplasm Potassium was retained in excess of the figure calculated from the nitrogen balance, while the phosphorus retained largely corresponded to the calculated amount The excess potassium corresponds to 1 3 and 0 5 kg of "wet glycogen" in case 1 and 2 respectively

Calcium balance (table II) —In both patients the urinary excretion of calcium increased The fæcal excretion of calcium, on the other hand, changed in opposite directions in these patients

Sodium and chloride balances (table III) —Both patients retained sodium and chloride, and increased their extracellular fluid volume as measured by the volume of distribution of chloride Both sodium and chloride were

TABLE III—CUMULATIVE BALANCES OF SODIUM AND CHLORIDE AND CHANGE OF THE CHLORIDE SPACE DURING ADMINISTRATION OF GROWTH HORMONE

—	Case 1	Case 2
Given GH for	12 days	16 days
Chloride space (litres)	+1 8	(+1 0)
Sodium balance (mEq)		
calculated from chloride space	+261	+145
actual balance	+397	+328
net balance (in relation to chloride space)	+136	+183
Chloride balance (mEq)		
calculated from chloride space	+180	+100
actual balance	+252	+144
net balance (in relation to chloride space)	+ 72	+ 44

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[3] Li, C H , Papkoff, H *Science*, 1956, 124, 1293
[4] Greenspan, F S , Li, C H , Simpson, M E , Evans, H M *Endocrinology*, 1949, 45, 455

retained in excess of the retention calculated from the change in extracellular volume It should be mentioned that in both patients perspiration increased during the treatment period

The rapidity of the changes in the balances induced by GH administration and withdrawal is illustrated in fig 1

Other metabolic effects—In case 1 there was a striking increase in the urinary excretion of acetone, and a disappearance of a pre-existing creatinuria (fig 2) Discontinuation of the hormone was followed by a return of acetone excretion to the pretreatment level, while the creatine excretion increased far above the level of the control period

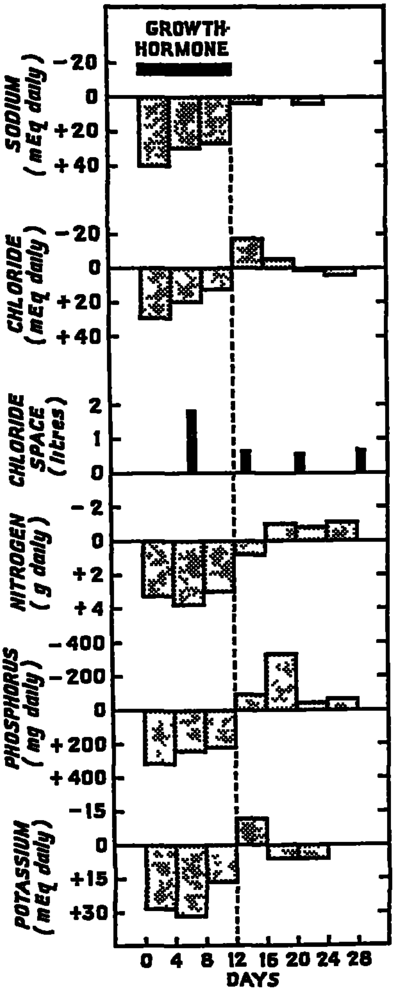

Fig 1—Changes in the balances of nitrogen, phosphorus, potassium, sodium, and chloride and the volume of distribution of chloride during and after administration of growth hormone in case 1

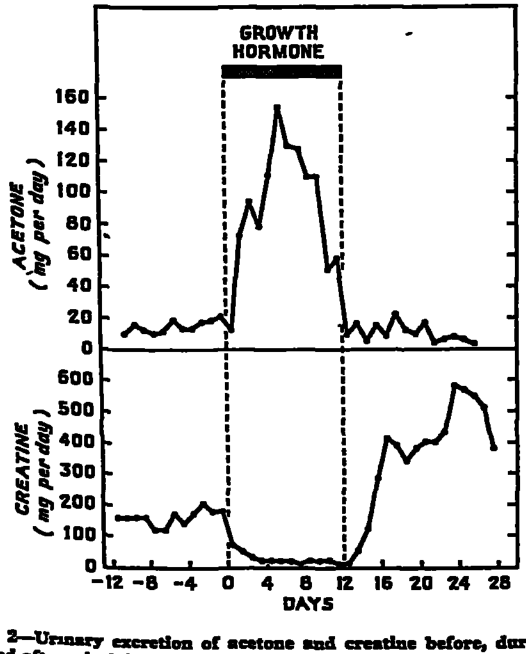

Fig 2—Urinary excretion of acetone and creatine before, during and after administration of growth hormone in case 1

In case 2 the creatine excretion was normal, and did not change, nor did the excretion of acetone change during GH administration The plasma levels of inorganic phosphate as well as of sodium, potassium, chloride, and calcium were unaffected by the hormone

Clinical effects—Both patients, especially case 1, showed increased perspiration, transient nervousness, and tachycardia as well as a feeling of satiety Furthermore, their daily consumption of water increased and the urine volume decreased No rise in temperature was noted, and blood-pressure remained unchanged There was no reaction at the site of injections

SUMMARY

Growth hormone purified from human pituitaries had a pronounced metabolic effect in two human subjects A daily dose of 10 mg produced retention of nitrogen, phosphorus, and potassium, retention of sodium and chloride together with an increase in the extracellular space, and increase in the urinary excretion of calcium In one of the subjects the excretion of acetone in the urine increased greatly and the creatine excretion, which was abnormally high, fell to normal during the hormone administration

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EFFECT OF HUMAN GROWTH HORMONE IN HYPOPHYSECTOMISED DIABETIC SUBJECTS

THE "diabetogenic" effect of pituitary growth hormone (GH) in animals has been well documented[1-3] but very little is known about this "diabetogenic" effect in man GH purified from animal pituitaries has been used in metabolic studies in man, but the results obtained were either negative or inconclusive[4] It was shown later by Li and Papkoff[5] that GH purified from human pituitaries differs in chemical and structural properties from the ones purified from animal glands

In the previous communication[6] we showed that human GH was metabolically active in man In order to investigate the "diabetogenic" action of human GH, its effect on three hypophysectomised patients with diabetes mellitus was studied

The patients were a 35-year-old male (case 1) and two females aged 28 and 25 years (cases 2 and 3) All three had been hypophysectomised for about four, three and a half, and three and a half years respectively because of severe vascular complications (retinopathy, nephropathy, and neuropathy) Case 1 was receiving at the time of the present study a standardised diet and 48 I U of insulin Leo retard Cases 2 and 3 were studied under the conditions of a complete metabolic study The insulin requirements were 24 I U 'Novolene' for case 2

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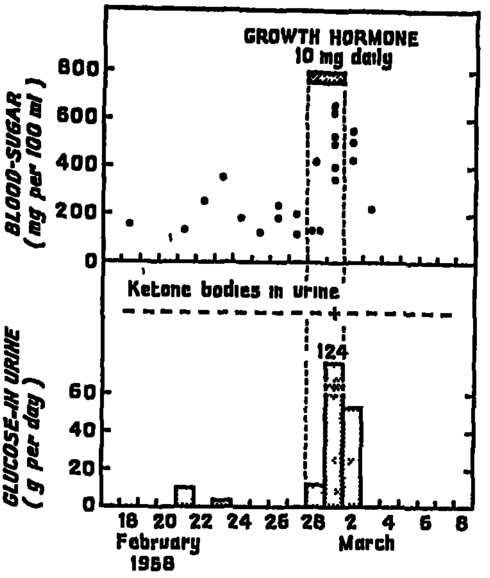

Fig 1—Blood-sugar level and urinary excretion of acetone and glucose in case 1 before, during, and after administration of growth hormone

and 24 I U protamine zinc insulin for case 3 Their remaining substitution therapy was as follows

	Case 1	*Case 2*	*Case 3*
Cortisone (mg per day)	50	25	25
Thyroid extract (mg per day)	120	120	120

The GH used was prepared as previously described[6] Biological assay in hypophysectomised rats by the tibia test[7] gave the following results

Preparation	*Total dose (μg)*	*No of assay rats*	*Average tibia width* (μ)*
325/58	25	4	219 ± 10 1
325/58	100	4	279 ± 12 2

* Mean ± standard error

The GH preparation was easily dissolved after adjusting the pH to about 7 0 GH was administered in a daily dose of 10 mg at 8 A M The duration of administration is shown in figs 1–3 No fever or local reaction at the site of injections were observed

RESULTS

In cases 1 and 2 (figs 1 and 2), the administration of growth hormone was followed immediately by a deterioration of the diabetic state as demonstrated by the increase in blood-sugar level and the appearance of pronounced glycosuria and ketonuria Because of the deterioration of the patients' condition, extra insulin had to be given in both cases 36 hours after the first injection of GH, the administration of which had to be discontinued In case 2, GH was given again 12 days later, and the same effect on carbohydrate metabolism was obtained

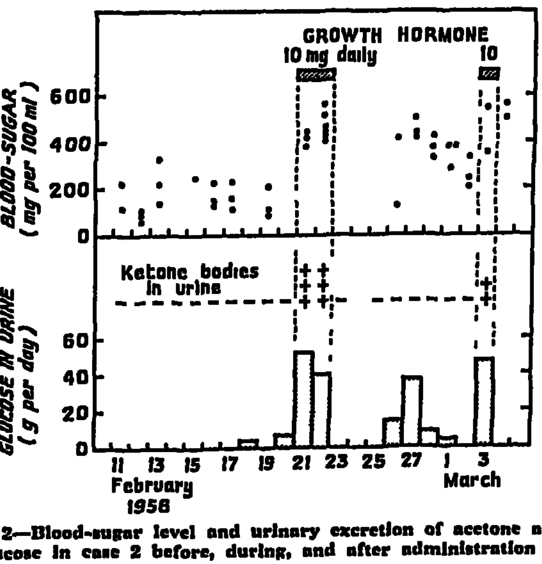

Fig 2—Blood-sugar level and urinary excretion of acetone and glucose in case 2 before, during, and after administration of growth hormone

The effect of GH in case 3 (fig 3) was similar though less pronounced Glycosuria and blood-sugar concentration increased during the first 24 hours, but pronounced ketonuria did not appear as promptly as in the other two cases On the other hand, even here the administration of GH had to be stopped on the eighth day because the patient's general condition had deteriorated so much

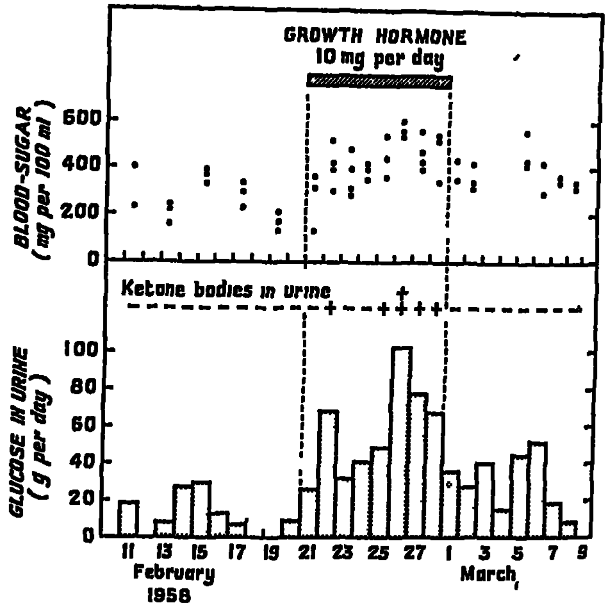

Fig 3—Blood-sugar level and urinary excretion of acetone and glucose in case 3 before, during, and after administration of growth hormone

SUMMARY

Growth hormone purified from human pituitaries was administered to three hypophysectomised diabetic patients In all three the hormone administration was followed by a pronounced increase in blood-sugar level, glycosuria, and acetonuria In two of the patients, the administration had to be stopped after 36 hours

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> "The adult, having asked a question, can hardly sustain sufficient interest in it to listen to the answer He may answer it himself or go on to some other irrelevant question If he can summon the effort to listen to the answer, he is likely to forget it as soon as he has heard it The child, strange and unaccountable as it may seem to us, asks a question because he really wants to know the answer Stranger still, he will listen carefully to a genuine answer, and, strangest of all, if it is genuine, he will remember it"—John Cohen, PH D *Humanistic Psychology* London, 1958

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[7] Greenspan, F S, Li, C H, Simpson, M E, Evans, H M *Endocrinology*, 1949, 45, 455

New Inventions

MODIFICATIONS OF A SPIROMETER FOR TIMED CAPACITY AND MID-EXPIRATORY FLOW MEASUREMENTS

THE percentages of the total vital capacity expired in 1, 2, and 3 seconds indicate the degree of obstructive impairment of ventilation (Gaensler [1]) Leuallen and Fowler [2] have shown the additional value of measurement of mid-expiratory flow-rates in early emphysema We describe here a simple modification of a spirometer in general use, which records the total vital capacity and any volume expired during a pre-set time-interval of 0 1–3 0 sec (in a similar fashion to the modification described by Gaensler) but in addition permits easy and rapid calculation of flow-rates from the start of mid-expiration

The only alteration to the ordinary spirometer is the insertion of a pin into the top of the counterweight to project horizontally through the slot in the counterweight cylinder The extra attachments (see figure) are

(1) A solenoid mounted on the bracket supporting the recording disc, in such a way that its rod holds the pointer When the solenoid is energised from the timer, the rod is raised and the pointer released

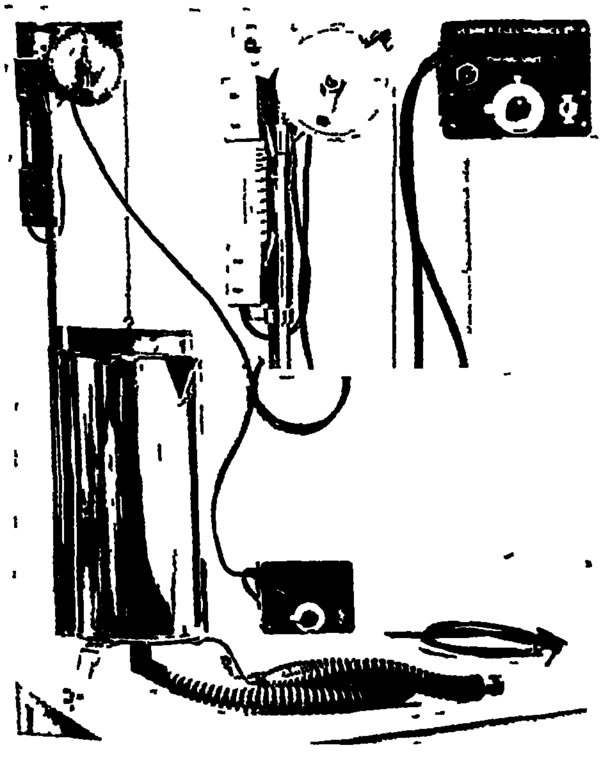
(2) A fixed microswitch mounted above and to the side of the counterweight and kept open, when the counterweight is at its highest position, by the counterweight pin

(3) A second microswitch, mounted on the side of the counterweight cylinder, can be moved on a scale calibrated downwards from 0 to 1600 c.cm

(4) A third switch, mounted above the fixed microswitch, determines which of the two microswitches is brought into operation

(5) An electronic timer graduated from 0 1 to 3 0 sec can be energised by a momentary electrical impulse

The end of the bracket supporting the recording disc acts as an indicator for the total vital capacity For timed capacity, the timer is set to the interval required, and the fixed microswitch is brought into operation As the spirometer bell rises, the counterweight descends, its pin closes the microswitch, and the timer is actuated The pointer is held until it has registered the amount expired during the set interval, after which the solenoid rod is raised and the pointer released to travel round with the disc For flow-rates from the start of mid-expiration, the movable microswitch is brought into operation and is then set to a position on the scale corresponding to a quarter of the total vital capacity This amount is therefore expired before the counterweight pin closes the microswitch Consequently the pointer registers the first quarter of the vital capacity together with the amount expired during the interval, after the first quarter, for which the timer is set (0 1–3 0 sec) By subtraction of the quarter of the vital capacity it is easy to calculate flow-rates from the start of the mid-expiratory phase



Timed capacity could, of course, be estimated solely by setting the movable microswitch to 0 on its scale On this machine two microswitches have been included to avoid having to set the movable microswitch to 0 after every estimation of mid-expiratory flow, and to avoid repeated settings of it, if it is desired to estimate the value of timed capacity after the expiration of certain fixed amounts

This modified spirometer is proving of use as an aid to clinical assessment, but it is hoped that its main value will be in the early diagnosis of emphysema and estimation of its progress, by enabling routine serial observations to be made on patients under supervision with chronic chest disease. Its simplicity of operation is a great advantage in outpatient work, where observations have to be made on many patients in a short time At this clinic health visitors have been trained in its use and make most of the estimations As it is an adaptation of equipment already in use, unnecessary expenditure has been avoided

The modifications were made by Messrs Venner Electronics, Ltd, New Malden, Surrey, and our thanks are due to Mr D R Ollington for his help

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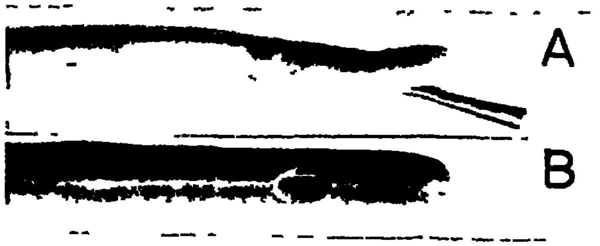
[1] Gaensler, E A *Amer Rev Tuberc* 1951, 64, 256

[2] Leuallen, E C, Fowler, W S *ibid* 1955, 72, 783

A MODIFIED FOLEY CATHETER

THE soft latex-rubber Foley self-retaining catheter is probably the most popular instrument for continued drainage of the bladder, but, unfortunately, in some cases its pliability makes its passage through the prostatic urethra impossible



To overcome this difficulty, a metal introducer is often used but, with the standard pattern of catheter, the tip of the introducer easily slips through the eye of the catheter and may injure the urethra (see figure, A)

A minor but useful modification of the catheter is shown in the figure, B In this pattern the eyes of the instrument are receded 2 cm from its tip, the end of the introducer sits comfortably within the cul-de-sac so formed without risk of displacement and can be used with complete safety

The catheter was made for me by Messrs Wm Warnes and Co and is a modification of the Warnes balloon catheter I wish to thank Mr E L Tugwell for the photograph

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Reviews of Books

An Introduction to Chest Surgery

GEOFFREY FLAVELL, F R C S , M R C P , thoracic surgeon, The London Hospital London Oxford University Press 1957 Pp 354 30*s*

THE rapid advance of chest surgery has made many books on this subject out of date before they are published, and it is hard to find one which can give the student and practitioner as distinct from the expert) an accurate picture of current practice

Mr Flavell and his publisher are to be congratulated on providing in this book the maximum information at the minimum cost The approach is practical, and after short ntroductory sections the author embarks straightway on how to look at a chest X ray, bronchoscopy, and pulmonary resections

The various conditions which may call for surgery are concisely discussed, and a number of short case-histories are added, to show how errors in diagnosis and treatment can arise and how they should have been avoided In the discussion on the diagnosis of bronchial carcinoma Mr Flavell points to an important fact even as recently as 1954 there was an average delay of over eight months between the first symptoms and surgical removal of the growth, and only one to two months' delay could be attributed to the patient Apart from diseases of the lung, there are adequate sections on the œsophagus and heart which discuss those conditions that can be treated surgically The final chapter, on mitral stenosis, is an admirable description of the disease and its possible remedy Clear line drawings and several pages of small but good X-ray reproductions illuminate the text

Here and there are matters about which other thoracic surgeons might disagree, but the balance of the book and its easy style should make it very acceptable to the general reader It gives an excellent picture of the scope of surgery in thoracic disease and provides much information that is not readily found in general medical and surgical textbooks

The Dynamics of Anxiety and Hysteria

H J EYSENCK, PH D , professor of psychology, University of London London Routledge & Kegan Paul 1957 Pp 312 32*s*

FROM time to time Professor Eysenck summarises in a book the work of his group at the Institute of Psychiatry (Maudsley Hospital) His latest instalment begins with a recapitulation of earlier work seeking to show that psychotic patients can be distinguished from those who are neurotic by their scores in a battery of objective tests, and that by further tests neurotic patients can be subdivided not only by their measurable degree of neuroticism or emotionality but also by their degree of introversion or extroversion Thus, hysterical patients are more extroverted than persons with anxiety states Professor Eysenck then passes on to a detailed analysis of the observed differences in learning, perception, socialisation, and response to drugs shown by the different personalities he has defined He measures the ease of acquisition or extinction of conditioned reflexes involving eye blinking, the rate of dark adaptation, attitudes to divorce and the death penalty, and nonsense-syllable learning while under the influence of amylobarbitone or dexamphetamine, and he interprets the results in terms of a neo-pavlovian theory of cerebral excitation and inhibition

The book is not easy reading Its chief value lies in its discussion of the experimental methods used, and the references to the fuller published papers of the Eysenck school The theory it proposes is still evolving, and unfortunately it appears so far to be moving along a different dimension from clinical psychiatry The author himself admits that it seems oversimple to explain the phenomena of hysteria and anxiety It must be added that the results on which it is based are statistical correlations between items of behaviour of groups of people Measurement of items of behaviour of an *individual*, with quantitative prediction of *his further* responses, is what interests the clinician, and general statements of probabilities in groups are of little use Professor Eysenck's ideas, however, have already stimulated a good deal of experimental work, and will provoke more, and that is sufficient justification for a scientific hypothesis If they could be applied longitudinally instead of cross-sectionally (that is, if the measurements were repeated at different times in the life of the same individual) they might come to have practical relevance

Bone Tumours

DAVID C DAHLIN, M D , consultant, section of surgical pathology, Mayo Clinic, Rochester, Minnesota Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1957 Pp 224 87*s* 6*d*

THIS is a study of 2276 consecutive bone tumours seen at the Mayo Clinic and no praise could be higher than that Dr Dahlin has done justice to such a rich source of material Anybody writing on bone neoplasms must come to terms with several problems to which there are as yet no satisfactory solutions Perhaps because there is often little correlation between the clinical course, histological structure, and radiological appearance of these growths, clinicians, pathologists, and radiologists have not yet agreed on a mutually acceptable nomenclature and without a common language it is hardly surprising that they have evolved no satisfactory classification Dr Dahlin bases his on a system suggested by Liechtenstein this has many features in common with Thompson and Turner-Warwick's classification and will be acceptable to most pathologists in this country The cell type is used as the chief criterion in assigning a tumour to its group this makes for histological accuracy, but it does not always favour clear distinction between what is clinically innocent and what is malignant

Tumours arising from marrow elements have been included in the survey malignant myelomas are, in fact, the largest single group The scope of the investigation can be judged by the fact that no less than 88 chordomas have been examined and analysed The lay-out and presentation of this vast material is impeccable and the illustrations have been judiciously selected and beautifully reproduced Dr Dahlin reaches no startling conclusions, but as a basis for further study his book will prove invaluable

Gastro-intestinal Obstruction

MEYER O CANTOR, M D , M S , F A C S , assistant attending surgeon, ROLAND P REYNOLDS, M D , F A C S , chief of surgery, Grace Hospital, Detroit Baltimore Williams & Wilkins London Baillière, Tindall & Cox 1957 Pp 565 144*s*

EVERY conceivable aspect of intestinal obstruction is here covered in a monograph by expert authors In a sapient preface they observe that, despite advances in the control of blood-chemistry by infusion and of infection by antibiotics, the mortality of obstruction can be reduced only by earlier operation

Starting at the œsophagus, they discuss obstruction at various levels of the alimentary tract Chapters follow on obstruction in special circumstances—in pregnancy, in infancy, and in the aged, for example—and then on procedures diagnostic, therapeutic, and operative The work would have been more effective if it had been more concise Emphasis is sometimes lacking, and it is hard at times to hold the thread Nevertheless as a source of information, with nearly 40 pages of bibliography (and over 40 references on each page), it excels

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Air Pollution (London Butterworth 1957 Pp 248 42*s*) —As Sir Hugh Beaver says in his foreword, "The question of Air Sanitation is one that affects the country from the social, medical and economic points of view, but it is essential that its consideration should be put on to a technical and scientific basis rather than an emotional one" A conference held at Sheffield University in September, 1956, sought to do this, and the papers (here edited by Prof M W Thring) discussed the nature, measurement, sources, course, consequences, and elimination of air pollution Dr John Pemberton gives an account of the ill effects of air pollution on health and vegetation.

THE LANCET

LONDON 5 APRIL 1958

The Twist of the Cord

No surgical emergency is more commonly misdiagnosed than torsion of the spermatic cord to suggest that 70% of twisted testes are lost because of delay in diagnosis may be a charitable underestimate Whether such charity is deserved is another matter The condition is eminently treatable when recognised in time, and the fact that patients with unilateral testicular atrophy do not usually realise that they are the victims of medical error is hardly a source of comfort

Torsion of the spermatic cord is uncommon (though not nearly so uncommon as hospital records would indicate), and it might be argued that little time can be devoted to it in undergraduate teaching But too much, not too little, is usually said It would be preferable to impress on the student simply that any painful swelling in the scrotum, or any scrotal swelling with abdominal pain, should be treated as a case of torsion unless some other cause is definitely established, and to add a word of warning about undescended testes Torsion conforms to no classical picture, nor are there characteristic features by which it can be excluded Many textbooks still maintain that the onset is usually sudden, but this is by no means so In a series of 31 patients, seen between 1943 and 1956 at the Radcliffe Infirmary, Oxford, SMITH[1] found that the symptoms had struck suddenly in only 14, and in 7 the first complaint had been dull abdominal or loin pain Such referred pain is a common diagnostic pitfall, and it is not confined to cases of incomplete descent Testicular pain is often felt at a point occupied by the testis in embryonic life—especially in the region of the internal inguinal ring[2]—and inflammation of the tunica vaginalis can simulate intra-abdominal peritonitis In the Oxford series strangulated inguinal hernia had been diagnosed in 5 cases, appendicitis in 2, and perforated duodenal ulcer in 1 Indeed, only 6 of the 31 cases had been diagnosed correctly before admission, and SMITH adds, in all fairness, that " the misdiagnosis [had been] several times accepted after admission "

The commonest, and in many ways the most calamitous, error is to diagnose acute epididymo-orchitis, and it is therefore not surprising that surgical teachers should concentrate on the differential features of these two conditions That such differences exist cannot be doubted, but it is debatable whether more harm or good is done by relying on them in everyday practice Mild trauma sometimes precedes torsion, and it may seem reasonable to postulate a mechanical cause of a mechanical disorder Yet this is in fact one of the armchair notions that prevent earlier diagnosis Life is marked by an uninterrupted succession of trivial injuries, and it is almost fatuous to name such pursuits as gardening or playing football as possible predisposing causes 2 of SMITH's cases were in jockeys, but neither of them had ridden during the twenty-four hours before the onset of symptoms In a 3-day-old baby who was known to have had torsion at birth " it was difficult to see any possible cause other than fœtal movements in utero " In 8 of his patients torsion started during sleep[1] Moreover, sudden physical strain, and a rise of pressure in the posterior urethra, has not yet been exonerated as a precipitating cause of acute non-specific epididymo-orchitis Slightly more valuable, though neither positively nor negatively diagnostic, is a history of previous warning episodes—sometimes only momentary and often amounting to no more than a " niggle " or a " twinge " However trivial these may seem, it is difficult to condone such terms as " cremasteric colic " or " testicular neuralgia ", even true anxiety symptoms are rarely referred to the scrotum Patients with recurrent subacute torsion form another small but characteristic group Occasionally the patient's age is of diagnostic help Epididymo-orchitis is exceedingly rare—and mumps orchitis practically unknown—before puberty, while torsion respects no age All observers agree that the peak incidence is between 13 and 20 years,[1 3-6], but middle-aged and elderly cords have been known to twist, and infants are frequent sufferers In a survey of 30 cases, seen at four Edinburgh hospitals in 1948–54, ROBB[7] records that 9 were between 15 and 20, 8 under 5, and 6 over 20, and SCOTT[3] mentions a 53-year-old patient who had had attacks of testicular pain at about two-yearly intervals since the age of 15 These workers note the absence of urinary symptoms before torsion, but such symptoms are not at all common in the early stages of epididymo-orchitis

Occasionally torsion can be diagnosed at a glance or by the lightest touch Far more often it is indistinguishable with complete certainty from epididymo-orchitis, and if the patient is to be treated conservatively nothing less than complete certainty is permissible Several eponymous physical signs bear witness to the clinical acumen of their originators—and to the difficulties they had themselves experienced The sign perhaps most widely known—that elevation of the affected testis tends to relieve the pain of epididimytis but to aggravate the pain of torsion[8]—may have statistical validity, but it would be most unwise to base on it alone a negative diagnosis SMITH[9] suggested that, for easier palpation, the cord should be infiltrated with local anæsthetic and OGILVIE[10] found diagnostic aspiration of the secondary hydrocele helpful But infiltration abolishes the patient's subjective response to pressure, and the characteristic bloodstained effusion in the tunica vaginalis may be slow to accumulate And there is the greatest urgency if the testis is to be saved " if you let slip time ", MILTON observed in a different context, "like a neglected rose it withers on the stalk" [11]

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[1] Smith, K H *Brit J Surg* 1958, 45, 280
[2] Brown F P *Brit med J* 1956, ii, 719
[3] Scott J E S *Postgrad med J* 1956, 32, 435
[4] Abeshouse B S *Urol cut Rev* 1936, 40, 699
[5] O Conor, V J *Surg Gynec Obstet* 1933, 57, 242
[6] Donovan, R J *Ann Surg* 1930, 92, 405
[7] Robb, W A T *J R Coll Surg Edinb* 1957, 2, 71
[8] Prehn, D T *J Urol* 1934, 32, 191
[9] Smith G I *Calif Med* 1953, 78, 506
[10] Ogilvie, W H *Ann R Coll Surg Engl* 1948, 2, 219

In a densely populated country it should be possible to send every patient to hospital on the slightest suspicion, thus giving surgeons a chance to operate immediately *Manual* untwisting is still recommended by some as a possible alternative [12, 13], but, though the method scores an occasional success, the successful performer is usually the patient rather than the doctor After several subacute episodes some men acquire a knack in this manœuvre, and the medical amateur will be most unwise to persist in his efforts once the expert has failed Time is better spent in arranging for the patient's *immediate* transfer to hospital For the journey all he needs is a sedative and a suspensory bandage, to apply hot-water bottles—as is done often by patients, and occasionally by doctors—is as irrational as warming the limb threatened by gangrene If in hospital the diagnosis is confirmed, or if doubt persists, the scrotum must be explored Conservative treatment has been advocated for infants, on the questionable ground that in them the diagnosis is always late [14], and some surgeons feel that conservatism is justified in old people Unfortunately, in the elderly torsion is liable to progress to septic necrosis and gangrene For the patient the operation (which can be performed under local anæsthesia) is trivial From the surgeon it requires scrupulous asepsis, gentleness, and a thorough knowledge of normal and abnormal scrotal anatomy The majority of torsions affect abnormal testes, and even normal landmarks may be obscured by swelling and congestion

The most important anomaly in the ætiology of this disorder is complete investment of the testis and epididymis by a capacious tunica vaginalis [15-17], or the whole scrotal contents may lie free within the scrotum, resembling the condition described in normal infants by ASTLEY COOPER [18-20] In G I SMITH's series of the 25 cases in which the site of torsion was recorded it was extravaginal in 22, and (contrary to the opinion of earlier workers [21]) there is little doubt that the first two centimetres above the tunica vaginalis is the segment most commonly involved Rarely the testis rotates around an abnormally long or mobile mesorchium, and multiple twists have been described [22] Testicular torsion (in both its acute and recurrent subacute forms) may be indistinguishable clinically from torsion of a *hydatid of Morgagni* In the latter disorder at operation the greatly enlarged plum-coloured appendage can be a perplexing finding, but the surgeon must not rush into an unnecessary *orchidectomy* Also hard to diagnose is the rare case of testicular rupture and here too excision of the prolapsed tissue and suture of the tunica albuginea (rather than removal of the organ) may be the best course to follow [1]

Earlier workers laid stress on the prevalence of torsion in undescended testes SCOTT concluded that "approximately 50% of cases of torsion occur in cryptorchids, and, as the undescended testis is found in only about 0-2% of all men, this is a predisposing factor" [8] Greater awareness of scrotal torsion will almost certainly lead to revision of such estimates [23, 24] The complication may be slightly commoner in incompletely descended testes, but only in proportion to the frequency of incomplete descent, and some of the difference may be due to the fact "that one of the common misdiagnoses is strangulated inguinal hernia, a condition calling for immediate operation which reveals the true state of affairs" [1] Malignant tumours of the testis account for many intra-abdominal torsions [25], nor is this association unknown in the fully descended organ [26, 27] Another disputed feature of this condition is its alleged right-sided preponderance [28] The distribution was approximately equal on the two sides in ABESHOUSE's and in G I SMITH's series, and SMITH feels that there is "no good reason why one side should be affected more often than the other" It may be worth recalling, on the other hand, that congenital herniæ and incompletely descended testes are commoner on the right than on the left side

When the testis is viable some form of fixation is the obvious procedure of choice [29] When viability is in doubt it may still be wise to leave the ischæmic organ behind and to counter the threat of infection by conservative means, endocrine function is apparently preserved in some glands which have lost their power of spermatogenesis Bilateral torsion is not common (5-10% seems a reasonable estimate [30]), but, especially where one organ has already been lost, there is every reason to advise prophylactic fixation of the other

The British Pharmacopœia

THE publication of a new *British Pharmacopœia* is a matter of considerable moment in the medical world Even though the practising doctor obtains his information about pharmaceutical preparations from other—and less austere—literature, sooner or later his prescribing habits are affected by the crystallisation of therapeutic opinion which occurs every few years between the covers of the *B P* and the *Addendum* It is true that additions and deletions are so numerous that a *Pharmacopœia* might be regarded as a public declaration of a Commission's fallibility But the book represents objective opinion at the time of writing, and in these days remarkable developments are possible in the few years between official pronouncements

The influence of the *British Pharmacopœia* extends far beyond an implicit recommendation of the drugs listed For well-nigh a hundred years it has been a recognised book of standards It symbolises much that is of value in the British tradition its status has been

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11 Milton, J *Comus*, 1
12 Burkitt, R *Brit med J* 1956, ii, 345
13 Smith, R E *Clin J* 1934, 63, 250
14 Glaser, S, Wallis, H R E *Brit med J* 1954, ii, 88
15 Muschat, N *Surg Gynec Obstet* 1932, 54, 758
16 Roche, A E *Brit med J* 1939, i, 27
17 Adams, A W, Slade, N *ibid* Jan 4, 1958, p 36
18 Cooper, Sir A Observations on the Structure and Diseases of the Testis London, 1830
19 Cooper, E R A *J Anat Lond* 1929, 64, 5
20 Campbell, M F *J Pediat* 1948, 33, 323
21 Ewert, E E, Hoffmann, H A *J Urol* 1944, 51, 551
22 Underhill, B *Lancet*, 1955, i, 129
23 Walton, A J *ibid* 1952, ii, 211
24 Bailey, H Emergency Surgery Bristol, 1953
25 Guice, E G *Ann Surg* 1954, 139, 524
26 Mohardt, D T *Ill med J* 1943, 84, 389
27 Babcock, J W *J Amer med Ass* 1916, 68 1699
28 Aird, I Companion in Surgical Studies Edinburgh 1949
29 Wheeler, J S, Clark, F B *New Engl J Med* 1952, 247, 973
30 Deming, C L, Clark, B G *J Amer med Ass* 1953, 152, 321

achieved through the disinterested service of a host of scientific workers who have looked for no reward beyond pride in a job well done. Admittedly, times have changed. The *B.P.* is no longer a catalogue of galenicals contributed by generations of empirical physicians. It is increasingly a compendium of pharmaceutical preparations included only after critical assessment by means of clinical trials, and the monographs and appendices create for the *B.P.* a unique position as a book of reference in laboratories as well as in the dispensary. This continuing revolution has been effected chiefly by the pharmaceutical industry—British and foreign. This point deserves emphasis. The new outlook in therapeutics has been made possible only by the vigorous application of scientific method and commercial enterprise. It is only fair to say also that the attitude of the pharmaceutical industry towards the Pharmacopœia Commission has been characterised by enlightened benevolence. All the leading firms have been quick to recognise the intrinsic worth of the *Pharmacopœia*, and they have encouraged their experts to help the Commission in every way possible. Further, they have regarded the inclusion of their products in the *B.P.* as a coveted token of official recognition of the therapeutic value of these preparations.

In this context, the *B.P.* 1958[1] may mark the end of an epoch. Among the "principal changes" to which reference is made in the introduction is the following statement regarding the use of colour:

> "Permission has been given in a limited number of monographs on tablets for the addition of a suitable colouring agent to the coating because unfortunately uncoloured tablets have not been made available. Similar provision has been made for some capsules."

The use of colouring matter in official preparations—except where there is a clear pharmaceutical justification—has been consistently forbidden by previous Commissions. The medical practitioner may be unlikely to regard this veto as of much importance if manufacturers prefer gaudy pharmaceuticals they are only falling into line with the confectionery trade and the motor-car industry. Nevertheless doctors must be increasingly aware that the polychromasia of the chemist's shop has introduced new hazards. The reference to a "principal change" is ominous, for clearly the commissioners were obliged to make a choice between principle and expediency. The manufacturers say in effect:

> "Here is a new drug synthesised and owned by our firm. It has been shown by rigorous clinical trials and by wide experience to be therapeutically valuable. You—the Pharmacopœia Commission—can hardly avoid including it in the next *B.P.* or *Addendum*. Now we, as the sole manufacturers, have decided to release this drug only in the form of a tablet with a coating artificially coloured blue. If therefore you include the drug itself in the *B.P.* you must accept our directions about the colour of the official tablet. If you publish in the *B.P.* a monograph describing the drug itself (a white powder) you will only make yourselves look ridiculous because we shall refuse to supply the preparation in any form other than that of the blue tablet. We know that when we first marketed this drug as a coloured preparation we did not follow the recommendations of the Commission, but we believe that by means of colour we can build up a conditioned reflex in the minds of patients and doctors whereby our tablet is favoured in prescribing for patients suffering from a common disease. This association of ideas is immensely important in the commercial world, so it must be allowed."

Though the permission now given to different manufacturers to market the same *B.P.* preparation in different colours may appear a small matter, it is quite a serious one if it means that the control of standards is no longer firmly in the hands of the commissioners. Someday a manufacturer may tell the Commission that there are so many coloured tablets that he has decided to introduce his new spasmolytic in the form of a crescent-shaped tablet because he has a special interest in the Oriental market. *B.P.* preparations of a new cardiac glycoside might be presented in heart-shaped tablets, and for a new diuretic preparation they might be reniform. These suggestions are by no means fanciful, for a manufacturer could justify his action by the kind of arguments used in favour of allowing colour.

We certainly do not suggest that standards and practices which differ from those of the *B.P.* are necessarily inferior. Further, there can be no quarrel with a manufacturer who deliberately disregards the rulings of the Commission and decides to go his own way. But having done so, he has no claim, we think, to ratification of his decisions by those whose standards are unrelated to commerce. The contribution of creative commercial enterprise to present-day medicine is very great, but its importance would not justify any weakening of the detachment with which the Pharmacopœia Commission have performed their different kind of public service. The printing of the Royal arms on their volume is evidence of their particular responsibilities as well as of their necessary privileges.

Support for the Family

TRADITIONALLY the good family has always looked after its weaker members—the old, the young, and the sick. The burden, even when willingly accepted, has often fallen unevenly, and in this century of small families, an ageing population, and working women, the system has shown signs of strain. Fortunately people have come to recognise that the larger society of the community, as well as the closer society of the family, has some responsibility for all its members, and the benefits of the Welfare State are the community's recognition of this duty. But the proper balance of responsibility between the family and the community is not easily reached. Over-protection can be a threat to the integrity and independence of the family. Indifference and lack of support may in the long run discourage even the most devoted relatives.

Some of the benefits which the State offers are dependent on a medical certificate, and because of this proviso and his knowledge of family circumstances the family doctor is well placed to judge how the scheme is working. Dr ASHWORTH in his survey of certification in a Manchester practice (p. 732) gives on the whole a good report, but he admits that a few of his patients' claims for sickness benefit were prolonged on social rather than medical grounds For instance return to work was sometimes delayed not by the worker's own illness but by the illness of other members of the family Concessions to domestic difficulties of this kind can be economical as well as humane, for the alternative is often a hospital bed, a home help, or a home nurse, any of which will probably cost the community more than an extra week or two of sickness benefit But if the need is real—and Dr Ashworth's examples suggest that it is—would it not be better to admit its existence and allow the doctor to authorise an official benefit to meet a family emergency? If, on a medical certificate, a healthy worker could claim an "emergency" benefit for a limited period of two or three weeks, to cope with a family crisis, the doctor need no longer uneasily feel that he is interpreting the rules of National Insurance rather freely The main difficulty, perhaps, would be the attitude of the employer, and of fellow workers, to this form of absenteeism Though in times of full employment many employers may allow their workers leave of absence under domestic duress, only a few of them, such as the London County Council, recognise it explicitly The majority view may be that industry cannot afford to encourage workers to leave their productive work, and admittedly the cost to the community through the loss of working time might well be heavier than the sums paid in actual benefit Even so, there might be a clear economic advantage through relief to the hospital and social services In the specially acute emergencies where a household is temporarily disrupted by the illness of the mother, an "emergency" benefit would make it easier for a husband, or a daughter, to take over the mother's duties temporarily, and, in days when help is hard to find outside the family circle, it might in fact be more useful than a benefit for the housewife in her own right, such as she has in Sweden

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[1] British Pharmacopœia 1958. London: Pharmaceutical Press for the General Medical Council. Pp 1012. £3 3s.

Besides emergencies, there are lasting disasters when some member of the family must give up work entirely so as to enable an invalid to remain at home Severely disabled war pensioners can already claim an attendant's allowance, but the middle-aged daughter who gives up her job to look after her mother who has had a stroke is forced to seek National Assistance In theory there is of course no reason why she should not, but in practice an official benefit would be a helpful recognition of her work and a token of the community's support and backing Indeed from time to time it has been suggested that a modest allowance should be offered to relatives who undertake the care of bedridden old people, and this proposal has lately been put forward again by Mr Peter Townsend [1] as a result of his survey of old age in Bethnal Green To say that a benefit of this kind would destroy the solidarity of the family is one way of looking at it Another is that it would be a supplement which the community would offer the family to enable them to keep the old person at home An allowance of this kind, backed by the assurance of a regular visit from a home nurse or a home help, and regular breaks when the old person could stay in a hospital (as in the scheme described by De Largy [2]), might go a long way towards solving the problem of our old people Admittedly the frailty of old age is not the only cause of a possible breadwinner being tied to an impoverished home other equally deserving people, such as widows or deserted wives with young children, have to turn to the National Assistance Board for help. But old people have the administrative advantage of forming a large and fairly compact group Undoubtedly also the provision of hostels and hospitals stimulates the demand for residential accommodation, and any alternative method of looking after our old people which would break this expensive and often second-best circle is worth considering

Another family question, more complex and more prickly, is also set by one of Dr Ashworth's cases In one family the father prolonged his sickleave to look after two children who were ill, because the mother would have lost her job had she stayed at home This arrangement may well have been the best to meet the emergency of illness But in this family in normal times the two parents were apparently in full-time employment No-one has anything but sympathy and respect for the singlehanded parent who is forced to earn a living for a family and run the home at the same time, but where there are two parents—at any rate while the children are young—a stable family background is usually best provided by a whole-time mother There are few hard facts about the extent of "mother employment" Custom probably varies from locality to locality, and circumstances from family to family An ablebodied grandmother, for instance, may be acting as a competent and loving locum tenens But the uneasy feelings of many who work among children, especially in industrial areas, were lately expressed by the Bishop of Woolwich in his Mothering Day sermon [3] He pointed out that half the women in industry today are married So large a proportion probably includes too many mothers, and he asked "How can there be a home life when children come home from school to an empty house when mother is too tired at the end of the day for either children or husband?" His plea has been reinforced by a Lancashire vicar [4] who estimates that 5% of the children in one of his church schools return to homes where no parent and often no adult awaits them In our own columns [5] a psychologist has expressed his reluctant acquiescence in the provision of day nurseries because the mothers need the money and the local industries the labour To offer a mother money to stay at home to look after her own children may seem extravagant, and probably only a fairly substantial subsidy would be effective The French system of offering mothers a *salaire unique* related to the minimum wage and the number of children is admittedly expensive, but, if we count the cost in insecure and unsupervised children, our own laissez-faire system may not prove cheap

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[1] Townsend, P Family Life of Old People London Routledge and Kegan Paul 1957 Pp 284 30*s*

[2] De Largy, J *Lancet*, 1957, i, 418

[3] See *Times*, March 17, 1958

[4] Tucker Harvey, V L *ibid* March 24, 1958

[5] Jones, H *Lancet*, 1957, ii, 739

Annotations

POSTOPERATIVE METABOLIC CHANGES

The metabolic effects of injury have not yet been fully defined Starvation is widely believed to play only a small part in bringing about the increased urinary excretion of nitrogen and potassium and the reduced output of sodium, injury is supposed to be the most important single factor in producing these changes But Dr Abbott and his colleagues, whose report we publish this week, believe that operative trauma and anæsthesia are only minor factors and that dietary restriction, complications, previous nutritional state, and age are the major factors

They describe observations on the effects of cholecystectomy in 11 women and 2 men who were placed on one of three types of dietary regimen for three days before and three days after operation, the two periods of observation were divided by an intermission of three to four days during which an ordinary full diet was consumed

When 5% glucose solution alone was given for three days operation had little effect on the excretory pattern of sodium, potassium, or nitrogen When sodium and potassium were administered in addition to glucose the postoperative variations were similar to those who received glucose only, except in one patient whose wound became infected In a third group of patients 5% protein hydrolysate and 10% fructose were added to the glucose, sodium, and potassium Although these patients produced larger volumes of urine than those in the other two groups their losses of sodium, potassium, and nitrogen and of body-weight were smaller Nevertheless the protein and carbohydrate supplied were evidently not wholly adequate, because even in the control period there was a nitrogen deficit and some weight-loss

That so little metabolic disturbance follows uncomplicated cholecystectomy is not very surprising and raises the question whether this operation causes sufficient damage to provide an adequate stimulus—adequate, that is to say, for present methods of measurement and detection of the items of postoperative metabolic variation This doubt is strengthened by the distinct effect of a pyrexial complication in one patient of the series, and by the authors' statement that a larger metabolic disturbance is associated with severe blood-loss, necrosis, or injection There is abundant evidence that after injury urinary nitrogen excretion is closely related to the previous state of protein nutrition and the plane of protein metabolism, and that in malnourished patients nitrogen excretion may increase little, if at all, even after very severe operations In well-nourished patients, however, provided the surgical injury is sufficiently severe nitrogen output usually increases notably Since in simple starvation the urinary nitrogen output usually declines and seldom increases, the large increase of nitrogen output which follows many major operations can hardly be attributed to inadequate diet

The report by Abbott et al raises again the important question of what part intravenous therapy should play in postoperative treatment The metabolic disturbances recorded here do not appear to demand intravenous therapy, which is expensive and not entirely free of the risk of complications, such as chemical thrombophlebitis The argument for such treatment would be stronger if there were larger differences between control and postoperative periods, and between the group who received glucose, potassium, sodium, fructose, and protein hydrolysate and the patients who received only glucose Until much more is known about the metabolism and excretion of adrenal cortical hormones and their end-products little is to be gained by discussing the apparent conflict between the observations of Abbott et al and of Moore et al [1] and Steenburg et al [2] on the relation of nitrogen balance to urinary hydroxycorticoid excretion The postoperative metabolic disturbances are likely to be due, not solely to "permissive" adrenal-steroid activity or to local tissue damage, but rather to a combination of both processes, and local damage is likely to prove the primary stimulus

LABORATORY SERVICES IN SCOTLAND

Laboratory services in Scotland have developed somewhat differently from those in England Clinical pathology as practised in England is a recent development in Scotland, where in the past laboratory investigations on patients were carried out mainly by university departments of pathology (which really meant morbid anatomy), bacteriology, and biochemistry, and in many hospitals hæmatology is still a province of medicine rather than of pathology Even now, a very large amount of the clinical-pathological work in Scotland is done by the university departments of pathology, and probably a larger proportion is done "postally" than in England, this is largely inevitable because of the sparseness of the population in many areas, but possibly there is still too much centralisation in the university laboratories Another difference is that there is no separate Public Health Laboratory Service, and public-health-laboratory work is carried out by the laboratories that are also responsible for the hospital laboratory work

A committee was set up by the Scottish Health Services Council in 1956 to consider the future of the laboratory service In its report [3] this committee recommends that regional plans should be developed for the hospital pathological work, so that university departments should do only such routine work as is necessary for teaching and research As regards administration of the laboratory services the committee, while admitting that a case could be made out for a regional pathological service centrally administered by the regional boards, felt that the existing service under the boards of management should be continued, but with the important difference that there should be more centralised planning of laboratory services by the regional boards with the advice of a strong pathological advisory committee, which would include members of the regional board, general practitioners, medical officers of health, and other consultants, in addition to pathologists

The committee insists that boards of management must be prepared to take account of matters beyond the local interest of their particular hospitals and proposes that the laboratories under more than one board of management be grouped to provide a more comprehensive service Although the expenditure on laboratories has increased proportionally nearly twice as much as expenditure in the hospitals generally, much still remains to be done, and the committee proposes that special revenue and capital allocations should be made to the regional boards for laboratory purposes and that regional boards should not have the power to divert these allocations to other purposes

Much of the report is of interest to hospitals in England and Wales In particular 'a wider grouping of hospitals than by hospital management committee areas to provide comprehensive specialist pathology services is very desirable many hospital management committees have tended to try to build up a self-contained laboratory service, even though special facilities can more economically and advantageously be provided by grouping with hospitals in neighbouring groups The direct allocation of funds specifically for laboratory development is also worth considering

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[1] Moore, F D, Steenburg, R W, Ball, M R, Wilson, G M, Myrden, J A *Ann Surg* 1955, 141, 145

[2] Steenburg, R W, Lennihan, R, Moore, F D *ibid* 1956, 143, 180

[3] Department of Health for Scotland Scottish Health Services Council The Organisation of Laboratory Services H M Stationery Office 1958 1*s*

The committee maintains that there is no case for a separate public-health service, as in England, and suggests that the future of the two existing public-health laboratories should be considered with a view to their full integration in the main laboratory service Many may feel that in England the separation of the Public Health Laboratory Service from the hospital laboratory service is in places too wide, and that much might be gained by unifying the service at the periphery

THE HAMMAN-RICH SYNDROME

UNDER the heading " acute diffuse fibrosis of the lungs " Hamman and Rich [1] described in 1944 a peculiar disease of the lungs, of which altogether 63 cases have now been reported [2] Since most cases have a subchronic or chronic course the adjective " acute " has been omitted in later reports, and the disorder is now referred to as the " Hamman-Rich syndrome " or " diffuse progressive interstitial fibrosis of the lungs "

The disease affects adults of all ages, only 2 cases in children have been reported [3,4] The youngest patient ($2^1/_2$ years) was that of Baar and Braid,[4] the oldest (72 years) that of Peabody et al [5] The onset is usually insidious The presenting symptom is progressive shortness of breath, which becomes associated with cyanosis Cough may be present from the onset, profuse mucopurulent, occasionally bloodstained, sputum is a comparatively late symptom Finger-clubbing was noted in about a third of all cases Cor pulmonale and right-sided heart-failure develop in the late stages Radiographic examination shows in only about a third of all cases the appearance of diffuse reticular striation of lung-fields, and occasionally this is associated with minute cystic spaces or fine honeycombing In the other two-thirds of cases there may be slight changes, such as mottled opacities in the hilar regions, or the appearance of congestion or of pneumonic consolidation may be found Histological examination shows diffuse changes in both lungs, although in different areas the lesions may be of different ages Everywhere the interstitial tissue, particularly the interalveolar septa, is broadened either by infiltration with monocytes, lymphocytes, and plasma cells or by fibroblastic proliferation with or without formation of collagen fibres The alveoli are usually lined by cuboid epithelium, they are either empty or contain a moderate number of alveolar macrophages Hyaline membranes may be present, but are seldom abundant Capillaries in the interalveolar septa may be obliterated [2]

Luchsinger et al [6] studied " cardiopulmonary " function in the Hamman-Rich syndrome They found restriction of the pulmonary capillary bed with resulting insufficient diffusion of oxygen The thickened interalveolar septa and the destruction of capillaries lead to reduced alveolar-capillary " contact-time " and so to what Austrian et al [7] named " alveolar-capillary block "

In differential diagnosis Baar and Braid [4] suggest that the following conditions be considered (1) chronic indurative pneumonia, (2) bilateral bronchiectasis, (3) atypical pneumonia, and (4) the so-called " rheumatic pneumonia " Such disorders as pulmonary hæmosiderosis, retrograde lymphatic spread of thymic carcinoma,[8] or syphilitic pneumonia are easily differentiated on clinical and morbid-anatomical evidence In several cases diagnosis was decided by means of lung biopsy This procedure seems to be justified, because some workers reported remissions or possibly arrest of the disease by treatment with cortical steroids or corticotrophin together with antibiotics [2,9,10] Others,[4] however, have observed no benefit with this therapy

The ætiology of the Hamman-Rich syndrome is unknown It may be significant that some patients have signs of hypersensitivity, and that a few show, in addition to diffuse interstitial fibrosis of the lungs, changes characteristic of " collagen disease ", such as " wire looping " of renal glomeruli, L E cells, and periarteritis nodosa Possibly allergy is at the root of the disorder There are some indications that, although the Hamman-Rich syndrome is a clinicopathological entity, it does not always arise from the same cause Thus the case of Callahan et al [11] was probably a pneumocystis pneumonia while the case of an infant described by Donohue,[12] which was probably an example of the Hamman-Rich syndrome in an early stage, presented the histological changes of interstitial plasma-cell pneumonia without pneumocystis

THE RUSSIAN VACCINE

ANSWERING questions about the Russian vaccine which has been used in the treatment of multiple sclerosis, the Minister of Health said in the House of Commons on Feb 24 that the evidence at present available was not sufficient to enable an opinion to be given on the efficiency or safety of this vaccine He added, however, that he was prepared to advise the release by Customs and Excise of small quantities imported for individual treatment on the advice of the patient's doctor His department would continue to gather all the information they could

There is indeed little published evidence at present The story began in 1946 with the claim by Margoulis et al [13] that they had isolated a virus which was neutralised by the sera of patients with multiple sclerosis, and subsequently Margoulis and Choubladze evolved a vaccine for the treatment of multiple sclerosis It was a suspension of brain tissue of white rats or mice infected experimentally with a virus of acute encephalomyelitis of man The virus was inactivated by formalin Last year Dick and his colleagues [14] in Belfast examined the properties of the virus concerned—the SV strain of E H A virus Their results suggested that it was rabies virus They were unable to demonstrate any specific neutralisation of this strain with sera from patients with multiple sclerosis, and they pointed out that the reported improvement of 30% of patients who had had the vaccine[15] was no more than might have been expected from the spontaneous remission of fresh lesions in untreated patients

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[1] Hamman, L, Rich A R *Bull Johns Hopk Hosp* 1944 74, 177

[2] Rubin, E H, Lubliner, R *Medicine*, 1957, 36, 397

[3] Bradley, C A *J Pediat* 1956, 48, 442

[4] Baar, H S, Braid, F *Arch Dis Childh* 1957, 32, 199

[5] Peabody, J W, Peabody, J W, Jr, Hayes, E W, Hayes, E W, Jr *Dis Chest*, 1950, 18, 330

[6] Luchsinger, P C, Moser, K M, Buhlmann, A, Rossier, P H *Amer Heart J* 1957, 54, 106

[7] Austrian, R, McClement, J H, Renzetti, A D, Jr, Donald, K W, Riley, R L, Cournand, A *Amer J Med* 1951, 11, 667

[8] Baar, H S *Öst Z Kinderheilk* 1954 10, 2

[9] Pinney, C T, Harris H W *Amer J Med* 1956, 20, 308

[10] Harris, M S, Preuss, F S, Goldman, A, Friedman, N *Amer Rev Tuberc* 1957, 76, 123

[11] Callahan, W P, Jr, Sutherland, J C, Fulton, J K, Kline J R *Arch intern Med* 1952, 90, 468

[12] Donohue, W L *Lab Invest* 1956, 5, 97

[13] *J Neurol Psychiat* 1946, 9, 63

[14] Dick, G W A, McKeown, F, Wilson, D C *Brit med J* 1958, i, 7

If the vaccine does in fact contain inactivated rabies virus, the Minister will be very reluctant to allow larger quantities to enter the country until the matter of its safety has been more closely examined The efficiency of the inactivation process must be assessed, and the risks involved in injecting brain tissue must also be weighed On the other hand, the interest which the vaccine has aroused springs largely from the sense of hopelessness which now surrounds the treatment of multiple sclerosis, and quite apart from the risk of concluding prematurely that the vaccine has nothing to offer, it is important to make plain to patients and their relatives in this country that every new idea is being carefully considered, even though the prospect is discouraging To make the course of justice more apparen in the case of this much-publicised vaccine the Minister might authorise the importation of a quantity for safety testing If the tests are satisfactory, clinical trials might then be arranged

MASSIVE VENOUS OCCLUSION

THE usual forms of thrombophlebitis are easily recognised, but the dramatic and often fatal blue phlebitis,[16] phlegmasia cerulea dolens, or massive venous occlusion,[17] is often confused with acute arterial obstruction The pathology of this form of phlebitis is not well understood, some cases are described in which the disease affected healthy people going about their usual routine, although in most instances it has complicated some other lesion The extensive venous thrombosis in this condition may plug the outflow by the major veins draining the leg, or by extending peripherally to the smallest radicles obstruct capillary blood-flow, a large volume of blood is thus dammed back and lost to the circulation, the oligæmia causes death in some 25% of patients, and gangrene develops in 50%[18] Edwards[19] has confirmed that the pressure in patent peripheral veins is extremely high, whether this high venous pressure is due partly to venospasm or whether there is associated arteriospasm is still disputed

Massive venous occlusion can be readily diagnosed when episodic attacks of thrombophlebitis have culminated in painful œdema of the limb, which is dusky The diagnosis is less easy when the disorder develops abruptly in a previously normal limb, but the severe pain, massive œdema, and turgid veins contrast sharply with the findings in arterial obstruction Treatment is by no means satisfactory Undoubtedly oligæmic shock must be rapidly corrected by transfusion, but the measures to be directed to the limb are less certain Those who believe that spasm is a factor in the persistence of the condition have advocated paravertebral block or spinal anæsthesia Edwards[19] was impressed by the improvement following spinal anæsthesia in 3 of his patients, although his continuous recording of venous pressure in the affected limb does not show convincing evidence of release of venospasm, whereas removal of an 8 in clot from the common femoral vein was followed by a considerable fall of pressure Thrombectomy has been carried out by others[20][21] and seems to be well worth while when it is feasible Veal[17] advocated a regime of passive exercise in the acute phase, with the purpose of pumping blood out of the limb, but this resulted in pulmonary embolism in one of Edwards'[19] patients

The value of anticoagulants is also disputed At the onset of the condition petechial hæmorrhages due to capillary hypertension may be present in the affected skin, and to increase clotting-time seems likely to worsen this bleeding tendency On the other hand, when thrombectomy has been performed or collateral channels have opened up, anticoagulant therapy may be desirable to reduce the liability to further intravascular clotting Even so, when by usual standards adequate anticoagulant therapy has been given, massive venous thrombosis has developed[19][22]

Though so little is known about the pathology of this disorder, and its treatment is far from satisfactory, early diagnosis can save life and minimise postphlebitic symptoms

SIR GORDON GORDON-TAYLOR

IN 1903 the University of London instituted the B SC. degree in anatomy The only candidates were two young men, Gordon Gordon-Taylor and Victor Bonney Being busy they decided to work through the night three times a week, sustaining themselves through the long hours by means of coffee essence heated over a Bunsen burner Both achieved first-class honours This story is told in the *British Journal of Surgery* for April, 1949, an issue dedicated to Sir Gordon, and last month, in honour of his 80th birthday, that journal once more honoured him by publishing a special Gordon-Taylor birthday number An introduction by Sir Cecil Wakeley, giving a brief account of his work, is followed by twenty-five articles on surgical topics by his associates and pupils The frontispiece is a reproduction of a portrait of Sir Gordon by Miss Anna Zinkeisen, which was presented to him at the Middlesex Hospital on March 27

The singleness of mind shown in his early anatomical studies has remained with him, and he has continued to work, write, and lecture Sir Cecil refers to his article on surgery of the innominate artery which dealt with work in progress when he was 72 Other topics on which he has written much and with great authority include hindquarter amputation, carcinoma of the œsophagus, and war wounds of the abdomen—he was consulting surgeon to the Fourth Army in the first world war and consultant to the Royal Navy in the second He has been a fellow of the Royal College of Surgeons for fifty-one years, he has been a vice-president, and has been vice-dean of the Institute of Basic Medical Sciences since its formation Surgery has been his life, though he was a classical scholar at Aberdeen before he began medicine, and he retains his love of Horace and is out of sympathy with some more modern, and perhaps more transient, entertainments He has done much to encourage young surgeons, and these and many others will join Sir Cecil Wakeley in his expression of esteem and good wishes to "the doyen of British surgeons"

DR CHARLES HARRIS has been elected vice-chancellor of the University of London for 1958-59

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[15] Choubladze, A Gaidamovitch S G *Mal infect* 1956, fasc II, 173
[16] Gregoire R *Pr méd* 1938, 46, 1313
[17] Veal J R, Dugan, T J, Jamison, W L, Bauersfeld, R. S *Surgery*, 1951, 29, 355
[18] Moser M, Babin S M, Cotts, G W, Prandone, A G *Ann intern Med* 1954 40, 361
[19] Edwards, W S *Surgery*, 1958 43, 153
[20] DeBakey, M, Ochsner, A *ibid* 1949, 26, 16
[21] Ellis, J T, Windham, S W *Ann Surg* 1952, 135, 262
[22] Catchpole, B N *Lancet*, 1957, i, 343

Special Articles

ABSENCE FROM WORK ON A MEDICAL CERTIFICATE

The Cost to Sickness Funds as seen from a General Practice

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THOUGH I regard it as my duty to see that my patient has all the treatment he needs, I also feel some responsibility for seeing that he returns to work as soon as possible and does not draw unjustly on the insurance funds to which we all contribute The family doctor is well placed to assess the true extent of unnecessary absence from work, and, as it is often said that this abuse of the welfare service is widely practised, I decided to analyse the information offered by my practice for the year May, 1955 to May, 1956

Facts and Figures

The practice has 3300 patients and is part of the Darbishire House Health Centre, established by the University of Manchester as an experimental teaching health centre The age and sex distribution of patients is similar to that in the country as a whole The average number of items of service per year given to each patient was 4

Because I practise in a health centre and in almost ideal conditions, my sickness certification is probably stricter than that of some practitioners, though I still have the usual types of excessively demanding patients

Unjustified Claims

In my practice, as in any other, there are the obvious malingerers, and in this investigation I counted 10 I refused sick notes to all these patients

Next came a group of 44 women and 54 men to whom I did issue sick notes although I felt they were extending their absenteeism beyond the time strictly necessary on medical grounds These women made 53 claims and lost 634 days' work unnecessarily, for which they drew £176 in benefit, the men made 61 claims and lost 640 days for which they drew £234 Of the 44 women 18 were in the fifty-one to sixty-five age-group

These women are an independent group They are mostly going out to work to earn money to buy the extras in life, and they seem to change their jobs often They soon seem to disagree with their employer or frankly have long periods resting, which go beyond what I consider reasonable Now, if a woman complains of feeling tired, I will always issue her with a sick certificate for a week or two, but if, after that time, she still shows no symptoms or signs of disease, then I regard her as probably unjustified in prolonging her claim

Among the men the age-distribution was fairly even Again, these men all had bad absence records

Justified Claims

In the same period 114 women and 209 men in my view claimed benefit honestly and did not absent themselves from work unjustly on medical grounds

These people had periods of sickness which were likely to be of limited duration and the list does not include those thought to have some disability which will permanently interfere with their return to work The women made 135 claims, and lost 3143 days, for which they drew £863 in benefit, the men made 270 claims, lost 6561 days, and drew £2505

TABLE I

—	No of patients	Women			Men			
		No of claims	Days lost	Cost (£)	No of patients	No of claims	Days lost	Cost (£)
Unjust claims	44	53	634	176	54	61	640	234
Just claims	114	135	3143	863	209	270	6561	2505
Chronic unemployable sick	15	15	4368	1265	17	17	5544	2450
Deaths	1	1	246	82	3	3	618	303
Total	174	204	8391	2386	283	351	13,363	5492

The Chronic Sick

This is a group of 15 women and 17 men who, as far as can be seen, are not likely to resume work again The group is not static, because from time to time patients do return to work, even after years away from it, but the list does not vary much The women lost 4368 days and drew £1265 in benefit, the men lost 5544 days and drew £2450 in benefit

Deaths

During the year under review, 1 woman and 3 men died, and they had drawn some sickness benefit

The Composite Picture

If we set these figures against the background of my whole practice we get a true appreciation of their significance In all, 457 men and women made 555 claims and drew £7878 in benefit Of these, 114 women made 135 just claims and drew £863, and 209 men made 270 just claims and drew £2505, in short-term claims of limited duration (table I) The justified sickness claims for men and women came to £3368 About half the sickness claims are for limited periods, and half the money paid out in sick benefit goes to a very small group of chronic unemployable sick patients

In my view 98 patients made 114 unjust claims which cost £410 Thus, out of every five people who made a claim, one made a claim which was unnecessary or unduly prolonged Of 21,754 days lost, 1274 were lost unnecessarily (table II)

TABLE II

Total no of patients claiming benefit	457	No of patients making unjustified claims	98
Total no of claims made	555	No of unjust claims made	114
Total days lost	21,754	No of unnecessary days lost	1274
Total cost in benefit drawn	£7878	Benefit drawn unjustly	£410

These are the tables which a businessman might draw up in introducing an insurance scheme into his own works But they take little notice of the social and domestic conditions of the patients After all, it may well be that some of these patients, especially the women, have home commitments which necessitate their absence from work, and it may even pay the community to allow them temporarily to be away from work and to pay them insurance while they are off work

Social and domestic circumstances sometimes provide extenuating circumstances which allow me to accept claims even though there are insufficient medical causes These domestic factors may not be sufficient to warrant the patient going to the National Assistance Board and there is often an interweaving of the functions of the doctor and the National Assistance officer

For example, a man stays off work to look after two sick children during Whitweek The wife says that if she stays off work she will be dismissed Obviously it is in the interests of all that I should cover this man with a sickness certificate It is the most expeditious way of dealing with the situation Again, an epileptic gets drunk on a Saturday night. He wets the bed in his lodgings and gets expelled from the house as a result. He gets aggressive and will not go to work until he finds fresh accommodation, and he wants to fight his employer anyway What else can I do but accede to his request for a sickness certificate?

I therefore looked at these claims again, this time with the eye of a humane family doctor to see how many cases had mitigating circumstances Apart from the chronic sick and the dying, I estimated that out of 158 women, 14 had periods of sick-leave justified on social or domestic grounds Similarly, 11 men had mitigating circumstances The amount of benefit these patients had claimed was £144

Discussion

Whenever I have discussed unjustified absenteeism with my colleagues, I have met with reticence Many pretend that it does not exist, since to admit it implies that certificates which the practitioner issues are not accurate. Some ask me "Who is to say that a patient is fit if he himself says he is unfit?"

Patients who say they are not well enough to work and yet the doctor feels they are, usually fall into the following group

Those who are blatantly trying to draw sick-pay under false pretences

Those who insist they are not well enough for work and yet are working at home for friends or relations

Those who are completing their fortnight on the sick-list so that they can claim their three waiting days

Those who are changing their jobs

Those who are extending a holiday—e g, Whitsuntide or Easter

Those with very mild symptoms

This last group cause the greatest doubts in my mind, but knowing my patients, and often seeing them in the street, or cinema, or public house, I can form a shrewd assessment of the strength of their claims

Extenuating factors operate more often in the women's claims, since women have so many responsibilities in the home to their children or to invalids Indeed, after reviewing the social background of some of the women claimants, one appreciates more than ever the tremendous load which some of them carry The wonder is that more do not have to give up their work. But the Government have repeatedly made it clear that the general practitioner is responsible for deciding whether or not a patient is fit for work, and I, for my part, have no difficulty in accepting the role of arbiter in these cases

About 1 in 5 claimants make claims which are unjustified, but in money they draw only £410 between them As the whole sickness claims over the year amount to £7878 we may conclude that only about 5% of the money paid in benefits is unjustly drawn. When account is taken of social circumstances this figure may be reduced to about 3% This low percentage is largely due to the very great drain on the sickness funds made by the chronic unemployable patients

Until I began this investigation I was not aware how big a drain these patients represent. Numbering only 32 (15 women and 17 men), those in my practice draw almost £3700 in a year, or as much as all the short-term absentees put together

These people have to come to terms with their diseases Their happiness in life depends on how they do this but many men fight on in a battle which gradually wears them down. They are often loth to surrender their jobs Sometimes it is possible to get a man to take over the household duties whilst the wife becomes the breadwinner, but most men regard this as an affront to their dignity Women seem to settle down more easily when once they have realised the chronicity of their complaint.

Doctors themselves become apathetic in their treatment. It is hard to generate enthusiasm in dealing with a patient who has attended regularly for years, and one colleague has suggested that any patient who is on the sick-list for more than a year should change his doctor Certainly the doctor needs to ask himself whether everything possible is being done for his chronic sick patients, not only in treatment but in the equally important realm of human relationships and social work.

The disablement resettlement officer has a part to play in trying to place these patients in work, but a closer link needs forging between this officer and the general practitioner The chronic-sick patient often becomes sullen and suspicious, believing that people think he is malingering But hope for the future lies rather in preventing patients from reaching this condition rather than in trying to rehabilitate them when they have got there Considering the cost of these patients in sickness benefit, the community would be justified in spending large sums if necessary in preventing incapacity

In these days of full employment we are employing people who once would not have been considered on the labour market and we must expect a higher sickness-rate than hitherto In global figures, in 1954-55 about £840 million was paid in sickness benefit My findings suggest that 3%, or £2½ million, was claimed unjustly This does not seem to warrant any radical change in our certification procedure On the contrary, it demonstrates how small a proportion of working people draw benefit wrongfully, and how well the people in this country play their part in the new social order

DOCTORS' PENSIONS

NEARLY every doctor in the National Health Service pays superannuation contributions After 10 years' service, if he is over 60, he becomes eligible for a pension, and with the approach of the tenth anniversary of the start of the N.H S, many of the more senior doctors will wonder where they stand The scheme is governed by regulations[1], two booklets explain the regulations concisely—one as they affect family doctors[2] and the other, more tersely, as they affect all N.H S employees[3]

The conditions on which a pension is paid are the same for specialists and family doctors, though the method of calculation may be different A pension and a lump sum (the retiring allowance, which has nothing to do with the compensation paid on retirement for loss of the sale of a practice) are payable after 10 or more years' service to a doctor aged 60—at an earlier age only if he is permanently incapacitated The normal "pensionable age" (i e, the age at which contributions cease and service is no longer reckonable in calculating benefit) is 65, a family doctor aged 60-64 may apply to the Minister to have his pensionable age extended to any up to 70 (The fact that the doctor has reached pensionable age does not mean that he can no longer practise) Other benefits provided under the scheme include an injury allowance (for those permanently incapacitated by injury sustained or illness contracted in the course of duty), a short-service gratuity (for those with 5–10 years' service retiring through incapacity), a death gratuity, and a widow's pension

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[1] National Health Service (Superannuation) Regulations, 1955 S.I 1955, no 1084 H.M Stationery Office 3s

[2] Barry H Superannuation for the General Medical Practitioner. London Heinemann Medical Books. 1955 Pp. 20. 2s. 6d.

[3] National Health Service Superannuation Scheme (England and Wales) an Explanation. H.M. Stationery Office. 1956. Pp 24. 1s.

The amount of benefit depends on length of service and amount of pay For a general practitioner the annual pension on retirement is 1½% of the total "superannuable remuneration" (see below) during the last 45 years of service, or the whole period of service if this is less than 45 years If he retires before 65 through incapacity, his pension is 1½% of his remuneration over not less than 20 years (unless he would have had less than 20 years' service at "pensionable age") The lump sum is 1½% of the total superannuable remuneration for married men and 4½% for others, if a man's wife has died or been judicially separated from him, the figure is 1½% for each year of service before the wife's death or separation and 4½% for each year after (The difference is because of the widow's pension liability) If a practitioner has completed 10 years of service, his widow is entitled to a pension, which is in general a third of the pension her husband might have expected, but if she is entitled in her own right to a pension in the same scheme, she is ineligible for a widow's pension (unless she is a practitioner, when she draws both pensions) A death gratuity is usually a year's remuneration or 1½% of the total remuneration, but benefits already paid are deducted from it

Full-time specialists (consultants and S H M O s), like other salaried staff, are entitled to a pension of $^{1}/_{80}$ (1¼%) of their "average remuneration" (i e, the average annual remuneration during the last three years of service) for each year of contributing service, to a maximum of $^{45}/_{80}$ The minimum pension for retirement through incapacity is usually $^{20}/_{80}$ of "average remuneration" The lump sum is $^{3}/_{80}$ of the "average remuneration" per year of service (up to 45), or $^{1}/_{80}$ for married men The death gratuity, widow's pension, and injury allowance are calculated on corresponding lines A part-time specialist has his benefits calculated in the same way as a practitioner's, unless he spends at least nine notional half-days a week as a specialist and has asked the Minister to direct that his benefits be calculated by the other method

For full-time specialists, "superannuable remuneration" means salary, for practitioners it means all payments by the executive council, less a deduction of the salary paid to any assistants, and of a sum representing practice expenses—50% of payments for mileage and pharmaceutical services, and 30% of most other payments In the case of a partnership, the remuneration is regarded as being divided equally among the partners unless they have elected otherwise

One or two examples follow

An unmarried family doctor who has served 10 years and in that time been paid £20,000 (£14,000 after deduction of practice expenses) will be entitled to a pension (1½%) of £210 p a and a lump sum of £630

A married family doctor with 10 years' service, who has been paid £35,000 (including £400 in mileage allowances) and has paid an assistant £10,000, will have a net remuneration of £17,360 His pension will be £260 8s, and he will receive the same sum as a retirement allowance If he dies, his wife will receive a pension of £86 16s (If this doctor had stayed in the service for another five years at the same rate of pay, these sums would all be 50% higher)

A full-time consultant, after 10 years in the hospital service and earning £3100 p a for the last 3 of them, would receive on retirement a pension of £387 10s

These figures are no more than a general guide, because there are many ways in which the position outlined above may be different in individual cases, thus service in the Armed Forces, employment of a trainee assistant, breaks in service, and the National Insurance scheme (those who opted for reduction of contributions on account of National Insurance will get a reduced pension) all affect the amount of pension payable A doctor who is uncertain about his own position can get information from the Secretary, Ministry of Health, Health Services Superannuation Division, Government Buildings, Honeypot Lane, Stanmore, Middlesex, or, in Scotland, from the Department of Health for Scotland, Health Services Superannuation Branch, Broomhouse Drive, Saughton, Edinburgh, 11

BRITISH PHARMACOPŒIA 1958

THE new edition of the *British Pharmacopœia*,[1] which will become official on Sept 1, includes 160 additions

New work on the clinical applications of antibiotics has led to the inclusion of tetracycline and oxytetracycline Phenoxymethyl penicillin and benzathine penicillin (tablets and also an injection) are added in recognition of the occasional justification of oral medication with penicillin

Experience of sensitivity reactions to local applications of penicillin doubtless accounts for the disappearance of penicillin ointments and cream from the official list Erythromycin becomes official Other antibiotics which are important but which have limited therapeutic uses are also included—bacitracin, neomycin sulphate, and polymyxin B sulphate The range of sulphonamides is increased by the addition of sulphamerazine and phthalylsulphathiazole Few will deplore the disappearance of sulphanilamide and sulphathiazole

Among the modifications of biological products is a new range of combined vaccines diphtheria and pertussis vaccine, diphtheria, tetanus, and pertussis vaccine, and typhoid paratyphoid A and B, and tetanus vaccine Human γ-globulin qualifies for official recognition as a safe and more effective alternative to convalescent serum in the prevention or attenuation of several infectious diseases of childhood

A considerable number of the new drugs listed are used principally in tropical medicine chloroquine, primaquine, and amodiaquine are antimalarials, chiniofon sodium is a well-established remedy for amoebiasis, dapsone and solapsone are of value in leprosy, lucanthone is used in schistosomiasis, and there are many others Hexylresorcinol, an anthelmintic in roundworm infestation, is reinstated Piperazine preparations, which have proved valuable in threadworm infestation, are also given a place

From the welter of anti-histamines those chosen by the Commission are antazoline, chlorcyclizine, diphenhydramine, and phenindamine Chlorpromazine is also included, though its antihistaminic action is relatively unimportant—compared with its uses as an anti-emetic, to enhance the effect of analgesic drugs, and in certain psychiatric disorders

Of the barbiturates, amylobarbitone, butobarbitone, and cyclobarbitone are added Barbitone and hexobarbitone go out It is odd that carbromal should have had to wait so long for official recognition as a relatively mild hypnotic Pentolinium (for arterial hypertension) becomes official just when it is losing ground in favour of mecamylamine—which may be expected to become official in the next *Addendum* The alkaloid reserpine, from the ancient drug rauwolfia, becomes official with a dose of 0 25–1 mg daily, but the need for conservative dosage—in order to minimise the risk of producing psychiatric disorders—may raise misgivings about the drug before the *B P 1963* is published

Endocrinology contributes the insulin zinc suspensions and preparations of hydrocortisone, prednisone, and prednisolone, and there is thyroxine sodium—a research tool rather than a necessary alternative to thyroid *B P* in clinical practice

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[1] This is discussed in a leading article on p 726

Neurologists have evidently convinced the Pharmacopœia Commission of the value of benzhexol, ethopropazine, and procyclidine in the management of parkinsonism, that mephenesin is worth a place in the treatment of tetanus, and that troxidone and paramethadione have, on balance, earned official approval in petit mal Suxamethonium chloride is already widely used by anæsthetists as a short-acting relaxant of voluntary muscle

New official drugs notable for their actions on the alimentary canal are the adsorbents (in gels and tablets) and spasmolytics such as propantheline bromide, and the revival of atropine methonitrate (now official) provides not only the physician's alternative to the Rammstedt operation but also the pharmacologist's oblique commentary on the spate of new synthetic spasmolytics The inclusion of procainamide—used as an alternative to quinidine to prevent bursts of extrasystoles—and of noradrenaline acid tartrate is not surprising, but the replacement of amphetamine by dexamphetamine must have called for nice judgment

Among the drugs which are best left in the hands of highly specialised practitioners is the cytotoxic substance mustine, used in Hodgkin's disease Folic acid has necessarily achieved official status, but its very limited applications have also been realised

The *B P* is by no means merely a physician's manual The surgeon will find here a number of interesting items including absorbable dusting-powder, absorbable gelatin sponge, oxidised cellulose, dextran, hyaluronidase, and diagnostic agents

Upwards of 130 drugs or preparations have been omitted Clove, fennel, nutmeg, and quassia all take their leave—no doubt to the chagrin of older practitioners who will find no consolation in the offer of sodium radio-iodide (^{131}I) and sodium radio-phosphate (^{32}P)

Other deletions which are significant of the climate of opinion in pharmacology and therapeutics are arsenic trioxide and the organic arsenicals, the bismuth salts, mercurous chloride, tincture of digitalis, spirit of ether, and serum gonadotrophin

Symposia

ANTERIOR-PITUITARY GLAND

A study group met at the Ciba Foundation, London, on March 11, under the chairmanship of Prof H L **Sheehan** (Liverpool), to review developments in knowledge of the anterior-pituitary gland

Hormone Content

Dr A. R **Currie** (Glasgow) reviewed factors affecting the yield of hormones extracted from human pituitary glands obtained within four hours of death Both the age and the sex of the patient influenced the content of gonadotrophins and of prolactin In pituitary tissue of women in the reproductive period of life the gonadotrophin content was relatively low, while in glands obtained from women at or beyond the menopause the yield was some three or four times higher than that found in premenopausal patients Gonadotrophic activity was also shown in pituitaries obtained from men, the content of stored hormone appeared to rise with advancing years Prolactin activity could not be detected in the glands of young men or of women before the menopause, but in postmenopausal women and in men over 50 prolactin activity was present, the amount being greater in women than in men In the case of the posterior-pituitary hormones, assays were conducted for pressor, antidiuretic, and oxytocic activities In all the glands studied the pressor activity closely paralleled the antidiuretic activity, while the relation of the pressor to the oxytocic activity was very variable The yield of posterior-pituitary hormones did not seem to be affected by age or sex or by trauma or other forms of "stress" immediately before death

Acromegaly

Dr P M F **Bishop** and Dr J H **Briggs** (London) discussed the prognosis in about a hundred cases of acromegaly 80% of these patients had died before the age of 60, most from cardiovascular causes They concluded that the modern treatment of acromegaly was not sufficiently radical and that a higher proportion of patients should be treated earlier by surgical means

Dr R **Luft** (Stockholm) believed that hypophysectomy was most likely to be helpful in acromegalic patients who had concomitant hypertension and cardiovascular disease Methods of assessing the activity of the disease were also discussed Prof A **Querido** (Leiden) had found neither the estimation of serum-inorganic-phosphorus nor the urinary excretion of creatine to be of any value in this respect Dr P J **Randle** (Cambridge) pointed out that the plasma insulin-like activity, determined by the rat diaphragm test, was considerably higher in acromegaly than in health, and suggested that this estimation might be a useful index of activity

Corticotrophin in Rheumatoid Arthritis

Dr **Oswald Savage** (London) reviewed his experience with long-continued corticotrophin therapy in severe rheumatoid arthritis In cases where, with such treatment, 17-hydroxycorticosteroid excretion rose appreciably, a satisfactory remission was usual If, on the other hand, the corticotrophin therapy had little effect on corticosteroid output, the course of the disease was usually unaffected Dr Savage concluded that mild adrenal stimulation was of value in relieving the symptoms of severe rheumatoid arthritis, and was more satisfactory than oral steroids

Gonadotrophins

Dr A C **Crooke** (Birmingham) said that in work on urinary gonadotrophins two assay methods were used, one depending on ovarian enlargement in intact mice treated with human chorionic gonadotrophin ("augmentation test") and the other on the mouse uterus test The former method had been claimed to be specific for follicle-stimulating-hormone (FSH) activity, the latter was not specific for either FSH or interstitial-cell-stimulating hormone (ICSH) and probably provided a useful index of "total gonadotrophic activity"

He reported parallel assays by the two techniques in a woman during the normal menstrual cycle, and claimed that the ratio of urinary FSH to urinary ICSH varied at different stages of the cycle Dr Crooke also described a method for the extraction of gonadotrophins from urine, based on the use of benzoic acid and tungstic acid, and claimed that this gave better yields than those obtained by the kaolin method

Dr J A **Loraine** (Edinburgh) questioned the specificity of the augmentation test and pointed out the advantages of using a method, such as the hypophysectomised-rat-prostate test, which was generally assumed to be specific for I C S H activity He suggested that the most satisfactory procedure for extracting gonadotrophins from urine was the kaolin-acetone method with appropriate pH control, including, in the case of low-titre urines, the tricalcium phosphate step

Anterior-pituitary Failure

Professor QUERIDO recalled that the earliest signs of pituitary failure were generally those due to absence of gonadotrophin secretion, and described a young woman and a young man showing hypogonadism only He also described a family in which two brothers had symptoms attributable to thyrotrophin deficiency alone and in which several sibs were found to have abnormally low levels of protein-bound iodine in the blood

Prof P A BASTENIE (Brussels) described the use of a "coefficient of ^{32}P exchange" by red cells as a measure of the activity of thyroid hormone

Prof R S MACH (Geneva) noted that aldosterone secretion, determined by urinary assays, continued in patients with panhypopituitarism

Report from Mayo Clinic

Dr E H RYNEARSON (Mayo Clinic) discussed the endocrine complications in 153 patients subjected to operations on the pituitary He emphasised that permanent diabetes insipidus was an unusual sequel except where damage extended high on the stalk

His colleagues at the Mayo Foundation had prepared differential suspensions of isolated anterior-pituitary cells, he showed illustrations of single acidophil, basophil, and chromophobe cells prepared from rat pituitary tissue

Dr Rynearson reported 153 cases of Cushing's syndrome, 33 of which were due to adrenocortical tumour In the remainder the cause was adrenocortical hyperplasia, and in 12 of these radiological examination showed the presence of a pituitary tumour Of these 12, 7 were treated by total bilateral adrenalectomy and only in these patients was there evidence of progressive enlargement of the pituitary tumour after operation In each of 5 pituitary glands subsequently available for histological examination, the predominant cells were found to be chromophobe

Dr LUFT remarked that in 5 of his patients with Cushing's syndrome there was evidence of pituitary enlargement, all were subsequently shown to have chromophobe tumours of the pituitary

Pituitary Irradiation

Dr J H LAWRENCE (Berkeley, California) described the results of pituitary irradiation in 50 patients mostly with advanced breast cancer The apparatus, an 800 meV cyclotron, provided a stream of high-energy α particles The total dosage administered to the pituitary ranged from 14,000 to 30,000 rads, but at present 22,000 rads was given over a period of two to three weeks Pituitary function was assessed by urinary gonadotrophin and corticosteroid assays and by radio-iodine studies In most cases it was found that pituitary activity declined some two months or more after treatment, but no attempt had been made to correlate the pre-treatment hormone levels with the response to therapy No permanent nerve-damage was noted, though in some cases there were transitory visual-field defects

Growth Hormone

Dr LUFT, working in collaboration with Dr D IKKOS and Dr C A GEMZELL, had observed the metabolic effects of human growth hormone (10 mg a day) in a healthy subject, a patient with rheumatoid arthritis, and 3 juvenile diabetic patients who had previously been subjected to hypophysectomy for vascular complications[1] In the healthy subject and in the patient with rheumatoid arthritis the effects of growth hormone were almost identical, and included striking retention of nitrogen, as well as some retention of phosphorus, potassium, sodium, chloride, and calcium After periods of treatment of sixteen and twelve days respectively there was some rebound loss of nitrogen In 2 of the diabetic patients administration of growth hormone was associated with rapid deterioration in their condition, blood-glucose levels rose sharply and glycosuria and ketonuria were much increased In view of these complications therapy had to be discontinued after two days In the 3rd diabetic patient there was evidence that the hypophysectomy had been incomplete, in this patient the deterioration under treatment with growth hormone was not apparent until the seventh day

Prof RUSSELL FRASER (London) referred to the effects of a similar growth-hormone preparation which had been made available for clinical trial in the United Kingdom by Prof F G Young and his coworkers in Cambridge Over very short periods of therapy results similar to those reported by Dr Luft had been obtained

Medicine and the Law

Medical Evidence of Diminished Responsibility

A LABOURER, aged 52, was convicted at Durham Assizes of the capital murder of a 15-year-old boy At the trial the defence of diminished responsibility, under section 2 (1) of the Homicide Act 1957, was raised, and he appealed against his conviction on the ground that the verdict of the jury rejecting that defence was unreasonable and not supported by the evidence

On appeal, his counsel said that three doctors were called for the defence The evidence of a senior prison doctor was that the labourer was a sexual pervert lacking in moral responsibility, with a mental age of less than 10 years The doctor had formed the view that the labourer was feeble-minded and had a psychopathic personality, and those two factors together constituted an abnormality of mind which substantially impaired his responsibility for his acts A consultant psychiatrist had concurred in that opinion, and a third doctor had come to a similar conclusion There was no medical evidence to the contrary Counsel submitted that on that evidence no reasonable jury could have found other than that the labourer had been suffering from such an abnormality of mind as substantially impaired his mental responsibility for the crime he had committed

On behalf of the Crown it was submitted that abnormality of mind was a variable and not a constant condition and therefore the onus was on the defence to establish to the jury on the balance of probabilities that at the time of the crime and not at any other time there was an abnormality operating on the labourer's mind which substantially impaired his responsibility It was perfectly open to the jury at the end of the medical evidence to say that they were not so satisfied The labourer's case must rest on the ground that the verdict was unreasonable

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[1] Preliminary communications by Dr Luft and his colleagues appear in this issue on pp 720 and 721

The basis of the medical evidence as to the abnormality of mind reducing mental responsibility was that it consisted of two ingredients—first, that the appellant was feebleminded and had the intellect of a boy of 10, and secondly, that he had a psychopathic personality As regards the latter, the medical evidence was that it was episodic and recurrent Taking into account the nature of the two ingredients constituting the abnormality and the whole of the circumstances of the case it was open to the jury to say that diminished responsibility had not been established To say that they must be bound by the medical evidence would amount to dispensing with a jury

The LORD CHIEF JUSTICE, after a short adjournment, said that the court would allow the appeal and substitute a verdict of manslaughter for the verdict of murder given at the Assizes The reasons would be given at a later date The sentence upon the appellant was that he would be imprisoned for 20 years

REGINA *v* MATHESON *Court of Criminal Appeal* Lord Goddard, *C J* Streatfeild, Donovan, Slade, and Havers, *J J* March 24, 1958 George Waller, Q C, and Peter Taylor (registrar, Court of Criminal Appeal), P Stanley-Price, Q C, and R Rawden-Smith (Director of Public Prosecutions)

E M WELLWOOD
Barrister-at-law

Diminished Responsibility Again

The new defence of diminished responsibility has been successfully pleaded in the case of Graham Harold Geer, a 17-year-old youth charged with the murder of his stepmother [1]

Counsel for the defence told the jury that they would have to consider three points before they could return the verdict he asked for They must feel sure that Geer was suffering from an abnormality of the mind at the time of the offence If that was the case, they must decide whether it was caused by a disease Thirdly, if it was abnormality of the mind causec by disease, did they think it substantially impaired his responsibility for the killing?

Dr F H Brisby, principal medical officer at Brixton prison, said that Geer had been under his care from March 1 to 6 He had found that Geer was suffering from schizophrenia at the time of the killing There was no doubt that the disease had impaired Geer's mind and had affected his responsibility for the killing

Dr T C N Gibbons, consultant psychiatrist at the Maudsley Hospital, appointed by the Home Office to examine the accused, said that he entirely agreed with Dr Brisby's diagnosis

The jury found Geer not guilty of murder but guilty of manslaughter in accordance with section 2 of the Homicide Act, 1957

The judge sentenced Geer to imprisonment for life, saying that he was concerned that there should be proper punishment and also provision for Geer's future "I feel it right that I should give you such a sentence as will enable it to be reviewed from time to time I hope some time, and not too long, it will justify those responsible for you to allow you out again "

Compulsory Blood-test Refused

A husband, who is petitioning for divorce on the ground of the wife's alleged adultery, asked the court for an order to compel the wife to submit herself and her child to a blood-test with a view to obtaining evidence of the child's paternity A Scottish judge refused to make such an order and his decision has been upheld by three appeal judges [2] In the words of one of the appeal judges, the proposed order would be "an invasion of private right which is not consistent with our present methods "

Lord Thomson said that the most plausible way in which the argument for the husband could be put was to say that, owing to a new medical technique, evidence might be made available which would assist the court in discovering the truth It was in the interest of justice that the truth should be discovered, this method was scientific and objective and it was just obscurantism on the part of a court to refuse to avail itself of it

His Lordship considered, however, that this way of putting the argument obscured and misrepresented the problems presented They were not asked to say anything about the value of such evidence What the husband was asking the court to do was to compel the opposite party to the action to bring forward evidence which under normal circumstances she would not be under any obligation to furnish Moreover, it was evidence which could bring little advantage to the defendant, whereas it might be used strongly against her

His Lordship also referred to the problem of enforcing such an order Enforcement would mean the compulsory infliction of a surgical operation—a minor one, no doubt, but nonetheless an invasion of the person of the wife—or, if the court were not prepared to go that length, it would have to regard her refusal as a contempt of court

As to the child, Lord Thomson said that it seemed to him impossible, on any view of the problem, to compel a third party to undergo an operation in order to provide evidence for a plaintiff or a defendant

Lung-cancer Damages Claim

A New Orleans woman is suing two American tobacco manufacturers for $700,000 on the ground that her husband died from lung cancer caused by smoking their cigarettes His vocal cords had been removed in October, 1954, because of cancer, and he died of lung cancer in July, 1955 The judge declared a mis-trial because some members of the jury had received telephone inquiries as to their smoking habits, the trial is unlikely to come up again before November [1]

The widow says that her husband died of lung cancer in 1955 after smoking two packets of cigarettes a day for forty years, and claims that the defendants were negligent in failing to give warning about the deleterious effects of their product The defence will, it is understood, be based on a charge of contributory negligence on the ground that the deceased did not exercise due care in his smoking habits

Public Health

Vital Statistics for 1957

IN his latest quarterly return [2] the Registrar General gives some provisional figures for England and Wales in 1957 The live-birth rate was 16 1 (highest since 1949) and the death-rate 11 5 per 1000 (0 2 less than in 1956) The infant-mortality rate was 23 0—0 7 lower than in 1956, the previous low record

In the last quarter of 1957 the influenza epidemic was manifest in the death-rates of 924 (450) per million from pneumonia and 496 (23) from influenza, the tuberculosis death-rate was 135 (112) (Previous year's figures in parentheses)

The population at June 30, 1957, is estimated at 45,043,000, it is expected to increase to 50,370,000 in 1997 The excess of females was 1,479,000 in 1957, this figure is expected to fall to 556,000 in 1997

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[1] *Kent and Sussex Courier*, March 21, 1958

[2] *Scotsman*, March 1, 1958

[1] *N Y Times*, March 23, 1958 *Times*, March 26, 1958

[2] Registrar General s Quarterly Return for England and Wales quarter ended Dec 31, 1957 H M Stationery Office Pp 26 2*s*

In England Now

A Running Commentary by Peripatetic Correspondents

"SHAN'T be long," said my friend, "the meeting will be over in half an hour and then we can have a gossip with the chaps " I sat down on the hard bench My eyes slowly became accustomed to the gloom I became aware that I was not alone Not by any means, for there in a gigantic glass case along the wall, unlit and unlabelled, stood glowering, not one, nor even two, but a whole row, almost a platoon, of giant skeletons I was suitably impressed My first thought was that some past member of the staff had been a gorilla hunter in his spare time And what a hunter, what a bag! For the five largest skeletons, if I was not mistaken, were clearly members of the same family

But on closer inspection I began to waver There were no bullet marks anywhere and in the case were several pygmy apes which no self-respecting gorilla hunter would ever shoot, much less put in a glass case So my thoughts turned to anthropologists, who, after all, are only frustrated gorilla hunters Could this be one of those demonstrations illustrating the Descent of Man? But if so, at which end of the series did one start? True the gorillas were right for size and one had the blackened teeth of a confirmed smoker, but on the other hand the only skeletons with measurable brain pans were the pygmies with long tails—the gorillas were just solid bone from the neck up It was all very difficult Also where was the photograph that tradition demanded showing the anthropologist, capped and gowned, with one hand laid fondly on the skull of the missing link? Where were the labels and the book of words? Whoever heard of an inarticulate anthropologist?

Perhaps, I reflected, it's only a job lot of monkeys After all, why should I expect a medical school of all places to keep its skeletons in cupboards? The minutes ticked on, thirty, sixty, ninety Could it simply be that the traditional way of shaking off the unwelcome visitor was to arrange to meet him here and then quietly disappear, leaving the exhibit to do the rest? I looked again at those empty orbits My spine sagged But I had maligned my friend "Ah there you are," he said, turning up only an hour late "Come and see this old photo of Bayliss and Starling and Sydney Ringer, look at those handlebar moustaches, doesn't that one look like a billiard marker? What about this?" he said proudly, knocking over a cup of tea and pointing to the framed strips of toilet roll on which the impecunious but resourceful young W B Cannon had traced his first radiographs of the stomach. "And," he concluded pointedly, "do stop walking around as though you were going to touch the ground with your knuckles It wasn't my fault the meeting went on so long Kindly remember that you are in England now "

* * *

John said we hadn't a hope in the M R C P because of lack of clinical material We are psychiatric registrars and our stethoscopes were seldom out of our pockets

"We'll find our own clinical material," I said

"Where?"

"Here, in the psychiatric clinic "

It was hard work at first, but it taught us to do thorough examinations quickly Gradually we built up our clientèle Even John was impressed at the amount of underlying pathology we found in psychiatric patients Monday was the day for our cardiac clinic Patients with murmurs in their hearts attended regularly and physical check-ups were combined with their usual treatment Tuesday was reserved for neurology, Wednesday for metabolic diseases, and Thursday for obscure physical signs On Fridays we salved our consciences and saw patients in physical health

Our knowledge of clinical medicine increased rapidly Moreover, during those months we correctly diagnosed five carcinomas, one endocarditis, and a parathyroid tumour, all in need of urgent treatment But the interesting result of our new methods was the improvement in the psychiatric condition of our "special" patients Even some of the chronics improved so much that reluctantly we felt obliged to discharge them

Now that we are M R C P s these unusual psychiatric techniques have been modified We couldn't keep it up for ever, but we regard it as a successful experiment from all points of view

* * *

I've got flu, and for four days my temperature has been over 101 I can't lift my head from the pillow, but during that time I have mapped out in my mind a new investigation on the development of antibiotic resistance in the staphylococcus, the plot and a lot of detail for a novel which I know will be a best-seller, and two anecdotes for the peripat When my temperature gets down to normal I know the investigation won't get much further, the novel idea will be dustier than its projected jacket, and the peripatetic contribution will be one of the ones the editor files instead of publishing But when I look back, I have discovered that, if I have made any original contributions to anything, the three I like best were all conceived when in bed with a cold Is it the idleness, or is it the temperature? You know the perennial argument on creative energy and the tubercle bacillus With tuberculosis a dying disease, are we to rely on the influenza virus for our inspiration?

* * *

Entering the field of clinical psychology for the first time one is faced by a bewildering array of tests, subtests, and questionaries measuring every imaginable (and the odd unimaginable) human function Clerical speed, finger dexterity, manual dexterity, and symbolical manipulation, to mention but a few, yield their secrets to indices of significance, deviation, and standard error *One is happily the donor rather than the recipient*, but even so the use of the vocabulary test is a humiliating experience, especially where the patient casually guesses his way to the bottom of the column and one has to consult a dictionary to know if he is right Sadly one discovers that I Q s of over 120 depend on a knowledge of words one has never heard of, let alone understood A post-psychological depression sets in, but as the delusions of inferiority recede one asks oneself "Why?" Our test-key tells us that "minatory" means "threatening" and "traduce" means "misrepresent" O K , so why bother with the former words at all? And the same to putative, heuristic, and the lot of the 120-plus words Some complex technical words are needed, and we are used, of course, to *professorial perorations (sorry, speeches)* which include the occasional lexicographic peculiarity In general, though, I feel that words incomprehensible to more than I in 400 don't help I have therefore devised *a formula for* dealing with semantic extravaganzas of obscure comprehensibility I call it the commonsense test (my sense being remarkably common) If I can't follow an author without dragging along the *Oxford Dictionary* (2 vols), I consider it's a lot of rot

* * *

The R S O was a gentle person, and it was with diffidence that he knocked on the door The Hospital Board was in full session

"I came about the operating-table, sir "

"Yes "

"It is a wooden one We've had it forty years, and it has none of the things operating-tables ought to have After forty years, you know, it's getting rather—high "

"I think you came to us last year about it, too, Mr ——?"

"Yes, actually, I did "

"We remember We pointed out then, of course, that a new one is expensive—most expensive But we are sympathetic about your request We will give it every consideration "

"Thank you, sir "

"All right, Mr —— *Good afternoon to you* "

"Shall I come next year, sir?"

"By all means, my dear fellow By all means "

A little later, with equal diffidence, he knocked on the door again The meeting was still in full session

"I came about the operating-table again, sir "

"Have we not met already on the subject, Mr ——?"

"But we've had it forty years It's a *wooden* one "

"And we have heard this already, Mr —— "

"Yes, sir, but the situation is somewhat changed I have just been to the theatre, and I have chopped it up Good afternoon to you, sir "

Letters to the Editor

CONSULTANT DISTRIBUTION, WAITING-LISTS, AND UNDEREMPLOYED SENIOR REGISTRARS

SIR,—Many fully trained senior registrars remain inadequately occupied while the profession and the Ministry fail to respond to the needs of the community or the plight of the registrars. However, facts are gradually emerging to prove the inequity of consultant distribution which many of us have suspected for years.

Replies from the Minister of Health on Jan. 26, 1958, elicited this information:

Region	*Waiting-list*	*Average annual cost of consultant salary per bed*
Manchester	56,734	£28.5
Sheffield	51,960	£33.6
N.W. Metropolitan	36,447	£45.8

On March 10 the following facts emerged in answer to a question on staffing of beds for mental illness:

Region	*Beds*	*Consultants as whole-time units*
Manchester	13,019	18
Birmingham	13,758	36
N.W. Metropolitan	11,848	42

These contrasting figures are extremely difficult to relate to community needs, for social conditions would suggest the probability of a higher morbidity incidence in those regions with the lowest consultant ratios. It is extremely difficult to hold the Ministry of Health responsible, for ten years regional boards have been at liberty to devote each year what was considered an adequate sum to provide for the expansion of consultant staffing. The total allocation from the Ministry may have been inadequate but the method of spending this total was within the boards' jurisdiction.

In many regions very powerful medical advisory committees have had great influence on board policies.

We in the profession have failed to equate consultant supply to the needs of the population. The Ministry has failed to give money, encouragement, and advice in the matter. It is essential that action should be taken to break this impasse. An impartial committee, under a lay chairman, should review the situation speedily and make proposals to the Ministry and regional boards which will ensure a balanced medical service and help to eradicate an unsavoury situation which is not inherent in a national health service.

Central Middlesex Hospital,
London, N.W.10

HORACE JOULES

*** Our parliamentary report on p. 748 gives regional figures for consultants and staffed beds.—ED. L.

A FUNCTIONAL NECESSITY

SIR,—The answer to the "registrar problem" is quite simple. After an aspiring specialist has completed the senior house-officer, registrar, and senior registrar appointments he should be eligible to be appointed "consultant." This appointment would be similar in status to that of assistant surgeon or physician in the teaching hospitals before 1948. There must be enough of these appointments to absorb every senior registrar. "Weeding out" should be done at registrar level. The qualifications and experience necessary for "consultant" would be those now found in senior registrars in their third or fourth year or in the better S.H.M.O. appointments. The salary scale would by present standards be in the range £1700 to £3000. At the age of 45 years or after 20 years in the specialty a limited number of consultants—say, 20%—who had exceptional qualifications or who had made valuable contributions would be eligible to apply for the appointment of senior consultant with a salary range of £3000 to £4000. This scheme would:

(1) Remove unsuitable specialist material at a level when it is not too late to go into general practice or allow aspiring general practitioners to take registrar appointments before going into general practice.

(2) Solve the problem of redundant senior registrars.

(3) Remove the unfair gap that sometimes exists between the well-qualified S.H.M.O. and the well-qualified consultant of about 35. Often whether a man is an S.H.M.O. or consultant is a pure gamble.

(4) Remove the iniquities of the merit-award system.

I might add that at the moment I have no axe to grind since I am a fairly contented S.H.M.O.—a rare bird, so it appears. I should rather wait a while as an S.H.M.O. at my present hospital than be a consultant at certain hospitals I know. But, of course, if my suggestions were put into practice I should be even more content.

Leicester

HUMPHRY B. KIDD

TREATMENT OF BREAST CANCER

SIR,—In your leading article of Feb. 1, you say that "a strong challenge [to Professor McWhirter] now comes from the Mayo Clinic" where[1] in patients treated mainly by radical mastectomy in 1941–47, the five-year survival was 59.3% as compared with 48.1% in McWhirter's group treated in the same period mainly by simple mastectomy and irradiation. You also say that "comparison between the figures from the Mayo Clinic and those from Edinburgh is difficult", because in the Mayo Clinic series cases not operated upon were not recorded whereas "257 inoperable cases were included in McWhirter's results."

In his article,[2] referred to by Berkson et al. of the Mayo Clinic, McWhirter breaks down his total experience into 3 categories:

1. Operable (by ordinary standards for radical mastectomy): 1063 cases, 58% living 5 years. (This figure is almost the same as the 59.3% survival-rate of the Mayo Clinic's radical mastectomy series.)
2. Locally advanced: 546 cases, 30% living 5 years.
3. Distant metastases: 273 cases, 4% living 5 years.

It is clear that Berkson et al. compared the results obtained in the Mayo Clinic's operable cases with a group of McWhirter's cases that included both locally advanced (inoperable) and operable cases. The result, therefore, is not (as you state) failure to consider "the 257 inoperable cases." It is total disregard for McWhirter's 546 patients with advanced and inoperable local disease.

Reference to McWhirter's tables and to the Mayo Clinic's tables of five-year survivals shows that similar results were obtained by the two different methods of therapy.

	Five-year survivals	
	Mayo Clinic	*McWhirter*
All operable cases	59.3%*	58%
All operable cases under 65 years of age	58.9%*	60%

* Operative deaths not included.

Again it appears that in breast cancer the selection of cases for comparison has more influence on published results than the method of treatment given.

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GEORGE CRILE, JR.

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1. Berkson, J., Harrington, S. W., Clagett, O. T., Kirklin, J. W., Dockerty, M. B., McDonald, J. R. *Proc. Mayo Clin.* 1957, 32, 645.
2. McWhirter, R. *Brit. J. Radiol.* 1955, 28, 128.

MITRAL VALVOTOMY AND PREGNANCY

SIR,—In their paper on mitral valvotomy and pregnancy, Dr Wade and his colleagues raise a number of points concerning which our experience may be of interest In their series of 12 cases of valvotomy during pregnancy there was 1 maternal death, a number of serious complications, and 4 cases in which stenosis of the mitral valve was not severe 2 cases of valvotomy during pregnancy were reported,[1] and of our 400 consecutive patients subjected to mitral valvotomy in the past seven years, 10 were pregnant at the time of operation In this series of 10 there have been no maternal deaths and no important postoperative complications The 3rd patient had relatively mild stenosis (2 cm), and it was her case which prompted a review of the criteria for operation These two series are small but the published cases now number 97, and the fact that there have been 2 maternal deaths and some serious complications suggests that there may be an increased risk in operation at this time In this particular age-group (under 45) and with sinus rhythm our operative mortality has been less than 1%

In regard to the 4 patients in whom the stenosis was not severe, Dr Wade and his colleagues state that operation would not have been advised apart from pregnancy and these patients could have been managed medically They also state that if symptoms are severe enough and the valve is technically suitable, valvotomy is the treatment of choice. However, as they indicate, the increased blood-volume and cardiac output which occur in pregnancy greatly increase the resistance to blood-flow at the mitral valve Therefore symptoms during pregnancy may be out of all proportion to the stenosis and are, in themselves, an unreliable guide to the benefit which may accrue from operation since it may not be possible to enlarge significantly an orifice which is only moderately stenosed In our opinion, the criteria for recommending operation during pregnancy are a history of progressive dyspnœa before pregnancy and objective evidence of tight stenosis—that is, an electrocardiographic pattern of right ventricular hypertrophy and radiographic evidence of enlargement of the pulmonary artery and its main branches Basal transverse lines from distended lymphatics and an increased pulmonary arterial pressure as recorded by cardiac catheterisation during pregnancy are as unreliable as the severity of the symptoms

The point as to whether the valve is " technically suitable " is also worthy of consideration because, in our experience, the concept of the " pliant valve " is open to question[2] It is true that it is among those with " clear signs "—i e , a loud first heart sound and opening snap and a rumbling mid-diastolic murmur—that valves readily amenable to valvotomy will be found, but in this group there will also be many with tough, rigid valves in whom it is difficult to achieve a satisfactory result All that can be done is to ascertain that the degree of stenosis is considerable and then the patient must have what amounts to an exploratory cardiotomy Fortunately, in most cases, despite a rigid valve, a worth-while degree of splitting of the commissures can be obtained, especially with the aid of a transventricular dilator, and substantial benefit follows However, it must be remembered that even a technically successful valvotomy usually leaves a valve which is far from normal, and this will account for the fact that fairly severe symptoms may recur during pregnancy despite operation

The natural reluctance of a mother to be parted from her infant in its first months is, as we have emphasised, in favour of valvotomy during pregnancy in suitable cases to avoid postponement of the operation for more than a year from the initial examination

In summary, then, surgery during pregnancy is undesirable unless the evidence for tight stenosis is based on severity of symptoms before pregnancy began or objective signs of longstanding pulmonary hypertension but if these are present there is no contraindication t operation and usually the time is domestically convenient

Edinburgh RICHARD TURNER

MODIFIED TRACHEOTOMY TUBE

SIR,—In your issue of March 15 (p 569), Dr Frank Wilson describes a modified tracheotomy tube, the essential feature of which is an opening on the convexity of the outer cannula that allows, when the anterior aperture is occluded, re-establishment of the natural airway through the larynx Tubes of this type were made for and used by me over twenty years ago in the treatment of laryngeal diphtheria[1]

In those days of fairly frequent tracheotomy some children had difficulty in dispensing with the tube, owing to spasm of the larynx or to fear of choking The special open-back cannula was devised to allow them practice in natural breathing while retaining the safeguard of the tracheotomy tube Somethimes this took several weeks, and one child of two years wore his tube for almost a year before discovering that he could do without it No special occluder was used one simply covered the aperture with a piece of adhesive plaster

I still have the tubes in my possession, but with the decline of diphtheria have had no occasion to use them for a very long time

Infectious Diseases Hospital,
Paisley WILLIAM NAPIER.

INFANTILE GASTROENTERITIS

SIR,—I am pleased to see that Dr Giles (March 8) acknowledges my position in the matter of the relationship of *Escherichia coli* to gastroenteritis, but I do not think I misrepresented him, although I am prepared to accept that he has changed his views since 1948 when he and Dr Sangster wrote[2] " In view of our failure to demonstrate the pathogenicity of the agglutinable coliform, the possibility remains that the organism is merely a constant concomitant of a hitherto undiscovered virus, comparable with the presence of *B suipestifer* in the virus disease of hog cholera All efforts to demonstrate such a virus have as yet been unsuccessful ", and again, " Recovery of the previously described type of *B coli* in the fæces of an infant suffering from diarrhœa affords, in our opinion, strong presumptive evidence of at least one variety of primary gastroenteritis, *but whether its presence in over 90% of cases is of true ætiological significance remains to be seen* " (my italics)

Dr Giles asks what are my reasons for doubt, despite the published work of the past ten years Most of this work merely aims at confirming the presence of *Esch coli* serotypes in the stools without attempting to explain their presence there I recall no fundamental work on the normal bacterial flora of the infant gut stemming from this When does this flora change and why? Does it differ materially in the breast-fed or bottle-fed infant? *Esch coli* is regarded as a normal bowel inhabitant what factors predispose to a change in its character? Why should it apparently behave so differently from other known bacterial gut pathogens, such as the salmonellæ and enteric groups?

For a fæcal-borne pathogen to travel through the air with the speed ascribed to it seems incredible, unless all rules of hygiene are disregarded The infant's stools are fluid and are not normally left long enough to dry, and dry dust seems the only valid medium Indeed Hutchinson[3] states that there is insufficient evidence to show that infection spreads in hospital by means of ward dust

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[1] Logan, A , Turner, R W D *Lancet*, 1952, i, 1286

[2] Turner, R W D , Fraser, H R I *ibid* 1956, ii, 525, 587

[1] Napier, W *Lancet*, 1937, ii, 673

[2] Giles, C , Sangster, G *J Hyg , Camb* 1948, 46, 7

A significant proportion of infants are symptomless excretors why should not this represent the normal? If not, what causes the change? Enteric viruses have now been recognised (e g, Echo group, poliomyelitis), and to my mind such a virus seems to explain the rapid spread and explosive outbursts better than a bacterium.

There are many other questions to be answered I can only echo Lord Evans' words[4] "It is difficult to be entirely convinced that what appears on the culture plate in the laboratory is necessarily the same as happens in the patient"

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Chadwell Heath,
Romford, Essex
I M LIBRACH

NYLON-DARN REPAIRS OF HERNIÆ

SIR,—Mr Doran (March 22) makes a plea for the scientific approach to surgical problems and immediately takes the very unscientific step of distorting the evidence to suit his argument. The claim which he attributes to me, that a chronic sinus with monofilament nylon is almost unknown, is a travesty of the statement which I made (Feb 22)—which was that a chronic sinus following the use of the finer sizes of monofilamentous nylon is almost unknown in my experience He claims that my findings were diametrically opposed to those of Mr Marsden (March 8)—and Mr Marsden himself appears to think so too—but as I see it we both found that thick monofilamentous nylon not infrequently caused chronic sinuses Indeed, the findings of all your correspondents on this subject are compatible with my observation that thick nylon sometimes causes sinuses and thin nylon does not

It appears, therefore, that the premise on which Mr Doran's disputation is based is false

Manchester
HERBERT HAXTON

THE DOCTOR'S ATTITUDE TO HIS PATIENT

SIR,—In his letters of March 1 and 22, Dr Ryle criticised Dr Clyne (Feb 1) and castigated Dr Pasmore (March 8) for views which he states "insist upon a subjective approach which withdraws psychiatry from the arena of science" He is all for "detached scientific observations of the cause of neurosis"—and who is not?

But the only instrument of the would-be detached scientific observer in this field, both for investigation and treatment, is his own personality, imperfect though that may be To use this as effectively as possible the personality must be studied, altered, and allowance made for individual bias How this can be done other than subjectively I do not understand

Although Dr Ryle writes in his first letter that "the doctor's personality plays a very important part, and should be understood", he underestimates the importance of this vital fact, and his belief that only some doctors need attempt to adjust personality difficulties is a delusion Doctors do not spring at birth like Athene from the head of Zeus, free from the disabilities of the unconscious mind We are made from the same stuff as the rest of humanity

By ignoring this Dr Ryle is not advancing to the scientific goal which he seeks, but is maintaining what is now an outmoded obscurantism, based on his earlier training, as Dr Pasmore deduces in his letter

Sittingbourne, Kent
F M MALLINSON

BED REST, THROMBOSIS, AND EMBOLISM

SIR,—Your leading article of March 1 surveys venous thrombosis and pulmonary embolism in patients at rest in bed after operation Like most British writers on the subject, you do not refer to pulmonary emboli that arise from unsuspected leg-vein thrombosis in patients who are not confined to bed, but who are walking about and doing their ordinary work Long recognised in America,[1] these are common enough in this country to be clinically important, and any attempt to explain pulmonary emboli must take them into account. In concentrating on the postoperative cases, which are only part of the picture, it may be that some ætiological clue is being overlooked Small pulmonary emboli in ambulant people are usually diagnosed as pneumonia (It is not so long since small postoperative emboli were similarly misinterpreted) Large ones, if not immediately fatal, may be taken for painless myocardial infarcts I record in the accompanying table details of 11 cases of this type referred to me during the past six years All had multiple emboli, and the legs were outwardly normal, except for varicose veins in case 9 Cases 1–4 have been published elsewhere.[2]

PULMONARY INFARCTS IN AMBULANT PATIENTS

Case no	Age	Sex	Clinical features	Outcome
1	47	M	Dyspnœa	Necropsy multiple emboli, thrombosis left soleus
2	50	F	Dyspnœa, triple rhythm, E.C G of acute cor pulmonale	Necropsy multiple emboli, thrombosis both popliteals
3	49	M	Pain, dyspnœa	Necropsy multiple emboli, thrombosis both femorals
4	47	M	Recurrent pneumonia ×5	Cure by femoral-vein ligation
5	66	F	Recurrent pneumonia	Necropsy, multiple emboli, thrombosis left popliteal
6	71	M	Pneumonia	Responded to anticoagulants
7	75	F	Dyspnœa	Necropsy multiple emboli, thrombosis left posterior tibial
8	66	M	Pneumonia	Necropsy multiple emboli, thrombosis femoral
9	36	M	Pleurisy ×2, lung abscess	Cure by ligation of common iliac vein
10	54	M	Pneumonia ×2	Cure by ligation of inferior vena cava
11	43	M	Pain, dyspnœa, 3 attacks, triple rhythm	Responded to anticoagulants

I have not included 16 patients admitted to my wards during the same period in whom pulmonary embolism had arisen, while they were ambulant, from an obvious swollen leg These were not severe, and rarely recurred Since diagnosis presented no difficulty, anticoagulant treatment was started at once

Pulmonary infarction from small emboli is marked by pain, hæmoptysis, and fever, with pleural rub or consolidation on examination Pneumonia suggests itself, but if the symptoms recur after an interval, and particularly if they change sides, an embolic origin must be considered and must not be discarded, as so often it is, because of the apparently normal legs The expected response to antibiotics is of course lacking The appearance of the chest radiograph is often inconclusive Large emboli differ in producing severe dyspnœa, jugular venous distension, and triple rhythm, without local signs in the lungs clinically or radiologically The electrocardiogram may help here in case 2 it was diagnostic, and in case 11 right bundle-branch block was a valuable pointer

When diagnosis was made I have relied on anticoagulants in the first instance, but recurrence after withdrawal of treatment has compelled interruption of veins in cases 4, 8, and 10 It is clear that some of these patients must have either permanent anticoagulant treatment or venous ligation No effective treatment had been undertaken in those who died

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[3] Hutchinson R. I *ibid* 1957, 55 38
[4] Evans H *Trans med Soc Lond* 1957, 73, 37

[1] Homans, J *New Engl J Med* 1934 211, 993
[2] Petch, C P *Arch Surg Chicago*, 1955, 71, 912.

Rest in bed played no part in the production of these invisible thromboses, which had such serious effects, nor did other factors that have been claimed to operate, such as sitting in cramped positions in cars or aircraft No instance of malignant disease appeared either in necropsy or follow-up To describe such thromboses as " spontaneous " is to beg the question of their origin to explain them might throw light on the even more serious problem of postoperative emboli

St Helier Hospital,
Carshalton, Surrey

C P PETCH

ESSENTIAL FATTY ACIDS, LIPID METABOLISM AND ATHEROSCLEROSIS

SIR,—In your issue of Feb 15 Dr Kinsell and his colleagues discuss the serum-cholesterol-lowering effect of certain fatty acids and make the surprising statement (p 338) that we (Keys et al) and Ahrens et al [1] [2] " have advanced the hypothesis that double bonds furnished by fatty acids are responsible for the effects observed—i e , sufficient oleate would be quite as effective as linoleate or arachidonate Our studies do not support such a hypothesis "

As a matter of fact, this question of effect or lack of effect on serum-cholesterol of dietary oleic acid has been a matter of friendly but rather vigorous controversy between Ahrens et al and ourselves for the past year, notably at major symposia organised by the American Medical Association Council on Foods and Nutrition (New Orleans, March 15, 1957) and by the American College of Physicians (Boston, April 10, 1957), and at the Cleveland Symposium on the Chemistry of Lipides (May 7, 8, 1957)

Shortly before the article by Kinsell et al appeared, the Cleveland Symposium was published [2] and in this Ahrens et al discuss our publications and views at some length and state that we (Keys et al) " conclude further that the mono-ethenoid acids (almost entirely oleic acid) are neutral or totally lacking in effect, since a term describing the content of oleic acid in the dietary fat need not appear in the prediction equations "

We have summarised [3] our analysis of the results in 41 sets of controlled dietary comparisons, each involving 12 to 27 men on each of two diets differing in fats, which yielded the prediction equation for the response of serum-cholesterol concentration to a dietary change in fats

$$\widetilde{\Delta}\ \text{Chol} = 2\ 73(\Delta \textsc{s}) + 0\ 01(\Delta \textsc{m}) - 1\ 31(\Delta \textsc{p})$$

where S, M, and P are the percentages of the total diet calories provided from saturated, mono-ethenoid, and poly-ethenoid fatty acids, respectively, and the Δs are the differences between the two diets being compared We noted that " The contribution of the term for ΔM is statistically non-significant and recomputation with this term omitted yielded the equation

$$\widetilde{\Delta}\ \text{Chol} = 2\ 74(\Delta \textsc{s}) - 1\ 31(\Delta \textsc{p}) \text{ "}$$

Further, we stated, " Whether the mono-ethenoids (essentially oleic acid) have any effect is uncertain, but if there is an effect it is certainly small " Full details of the diets, methods, findings, and statistical analyses in these experiments covering the period 1951–56 have been published [4] [5]

Kinsell et al , besides misquoting us, report two instances in which they compared the effects on serum-cholesterol of oleic acid and linoleic acid in the diet

In the first, in a boy aged 19, at the end of three weeks on a formula diet containing 80 g of ethyl oleate daily the serum-cholesterol level was about 65 mg per 100 ml higher than at the end of two weeks when the formula contained 80 g of ethyl linoleate

In the second, a diabetic patient on a similar formula diet had a serum-cholesterol of 270 mg per 100 ml at the end of a week when the daily diet contained 75 g of trilinolein, 235 mg at the end of two weeks in which the diet contained 75 g of triolein instead of the trilinolein, and 297 mg at the end of three weeks when 75 g of ethyl oleate was substituted

We regret that these observations scarcely qualify as acceptable confirmation of our own findings and interpretation, though they are not in opposition

More to the point are two new sets of data from our own controlled dietary experiments which will be reported in full in due course but may be mentioned here

First, a switchback dietary experiment on 22 men, rigorously controlled for six weeks, conclusively showed no effect on serum-cholesterol from substitution of 68 g of oleic acid glyceride daily for 612 calories of carbohydrate or from the reverse substitution [6]

Second, we now have 12 additional sets of dietary comparisons, each involving 5 to 25 men on each of two diets differing only in the kind of fat or in the isocaloric exchange of fat for carbohydrate in the diet Least-squares multiple regression analysis of the data in the same manner as reported previously [4] [5] produced coefficients in a prediction equation statistically indistinguishable from those found in the earlier 41 sets of experimental comparisons, and again the mono-ethenoid (oleic acid) variable makes no statistical contribution (i e , zero effect)

The conclusion is, as before, that saturated fats raise the serum-cholesterol level when isocalorically substituted for carbohydrate, that polyunsaturated fatty acids lower it, and that about 2 g of linoleic acid is needed to offset the effect of 1 g of stearic or palmitic acid Finally, and again as before, we conclude that oleic acid has no significant effect in either direction, oleic acid glyceride is substantially equivalent to simple carbohydrate in effect on serum-cholesterol

We have noted that oleic acid accounts for practically all of the mono-ethenoid fatty acid in the great majority of natural food fats and oils Rape-seed oil, which contains up to half of its fatty acids in the form of the mono-ethenoid erucic acid (a 22-carbon mono-ethenoid, docos-13-enoic) is an exception We have no experience with rape-seed oil, but the data in the recent report by Linko,[7] though inadequate for exact computation, suggest that erucic acid, like oleic, is " neutral " in respect to effect on the serum-cholesterol level in man

Ahrens et al [2] admit that their data are in conformity with computations from our prediction equation (published before their data appeared), but object that, " Keys' prediction could have been expressed just as accurately, and less mysteriously, in terms of iodine value of dietary fat " This is just as palpably erroneous as the misquotation of Kinsell et al The iodine value is, of course, merely a measure of the number of double bonds in 100 g of fat, whereas our equation ignores the double bonds in mono-ethenoid fatty acids and, in any case, refers to the amount of fat calories as a percentage of calories from all sources in the diet

Ahrens et al may have been misled by the fact that in their experiments, in contrast with our own, they usually deal with the same amount of total fat and vary only the kind of fat In that situation there is often a rough relationship between the iodine value and the expression 2S−P, which is an approximation to the right-hand term in our equation given above But even when the total fat is constant the iodine value does not correspond precisely with our formulation

Consider a 3000-calorie diet in which there is a total of 133 g of fatty-acid glycerides, half being saturated and half being linoleic acid Let us now change the diet only by replacing these fatty acids with 133 g of oleic-acid glyceride (i e , triolein) Note that fats yield

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1 Ahrens, E H , Jr , Hirsch, J , Insull, W , Jr , Tsaltas, T T , Blomstrand, R , Peterson, M L *Lancet*, 1957, i, 943
2 Ahrens, E H , Jr , Hirsch, J , Insull, W , Jr , Peterson M L *in* Chemistry of Lipides as related to Atherosclerosis (edited by I H Page), p 222 Springfield, Ill , 1958
3 Keys, A , Anderson, J T , Grande, F *Lancet*, 1957, i 787
4 Anderson, J T , Keys, A , Grande, F *J Nutr* 1957, 62, 421
5 Keys, A , Anderson, J T , Grande, F *Lancet*, 1957, ii, 959
6 Keys, A , Anderson, J T , Grande, F *Pro Soc Exp Biol* , *N Y* 1958 (in the press)
7 Linko, E *Acta med scand* 1957, 159, 474

1200 calories of the total 3000, or 40%, in both diets, and, in our terms, we have values of S=20 and P=20 with the first diet and S=0, P=0 with the second The iodine value will be identical in the two cases (=86) and, according to Ahrens et al , there will be no change in serum-cholesterol But the equation based on our experimental results predicts a serum-cholesterol change

$$\Delta \text{ Chol} = 2\ 74(0-20) - 1\ 31(0-20) = -29,$$

i e , on the average, the serum-cholesterol concentration will fall by 29 mg per 100 ml on the second diet.

Finally, we may consider a third diet which differs from the first only in that the total fat is only 67 g (20% of total calories) The iodine value is still 86 in both diets Ahrens et al apparently predict no change, or at least they provide no clue as to what may happen But our equation predicts

$$\Delta \text{ Chol} = 2\ 74(10-20) - 1\ 31(10-20) = -14,$$

i e , changing from the first to the third diet will, on the average, produce a fall of 14 mg per 100 ml

In view of the fact that the great current interest on these points seems to be matched by an equal degree of confusion in many quarters, we should point out that the prediction equation refers to the average changes in serum-cholesterol to be expected in men without a high serum-cholesterol within two to four weeks after a dietary change Larger responses may be expected in hypercholesterolæmia and also, perhaps, with dietary differences maintained for very long periods of time And, of course, there is no place here for speculations about "essential-fatty-acid deficiency"

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ANCEL KEYS
JOSEPH T. ANDERSON
FRANCISCO GRANDE

REDUCTION OF CIRCULATING LIPIDS

SIR,—With reference to the article by Dr Oliver and Dr Boyd[1] your readers may be interested to hear of our results in a similar therapeutic trial[2] with 2-phenyl-*n*-butyric acid amide *

Of 15 men with considerable hypercholesterolæmia, 12 had had a myocardial infarction between six weeks and a year previously, but had no signs at present of cardiac failure or of angina 1 had essential hypertension, another had essential hypercholesterolæmia without clinical manifestations, and 1 had hypercholesterolæmia with xanthoma tuberosum on the fingers and elbows The ages of the patients varied from 36 to 63 (average 50 6)

The dosage of 2-phenyl-*n*-butyric acid amide was 1 g every eight hours All patients were carrying on their usual occupations, no special diet was given, but they were asked to be careful not to put on weight. 1 patient received the treatment for four weeks, 3 for two months, and the others for from three to five months In 10 of the 15 patients, plasma-cholesterol level was reduced by 20 mg or more per 100 ml The initial mean total plasma-cholesterol in the 10 patients who reacted favourably was 346 mg per 100 ml., this dropped to 310 mg after giving the drug The mean initial absolute level of β-cholesterol was 310 mg per 100 ml., dropping to 258 mg after treatment (the β-cholesterol level was determined by analytical chemical methods after elution of the fraction from the paper after electrophoresis)

The average total plasma-cholesterol among healthy men of European Jewish origin in Israel in the age-group 40–60 is 220 mg. per 100 ml , and of β-cholesterol 180 mg , taking these levels as 100%, our results for the 10 patients were a drop in total cholesterol from 157% to 131% and a drop in β-cholesterol from 162% to 143%

The effect of 2-phenyl-*n*-butyric acid amide seems to be greater in patients with a high initial level of plasma cholesterol, 4 of the 5 patients who did not react to the treatment (and only 1 of the 10 who did) had an initial plasma-cholesterol less than 300 mg per 100 ml

Like Dr Oliver and Dr Boyd, we found hardly any change in the ratio between α and β cholesterol, even where there was a significant fall in total cholesterol We have noted this in other therapeutic trials for lowering the lipid levels, and it seems that the ratio of α to β cholesterol is one of the most stable factors of the lipid patterns

In none of the 15 patients did the lipid levels rise We infer that 2-phenyl-*n*-butyric acid amide has a genuine, though not great, cholesterol-depressing effect Our results are not so favourable as those of the French and Italian clinical workers,[3-6] but we believe that n-phenyl-*n*-butyric acid amide does have some effect, especially when the plasma-cholesterol is very high

Tel-Aviv
Jerusalem

DANIEL BRUNNER
K. LOEBL
L E SCHINDEL

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*Marketed as Nivonorm by Teva Jerusalem.

[1] Oliver M F, Boyd, G S *Lancet*, 1957 ii 829

[2] Brunner, D , Loebl W , Schindel L. E. (in the press)

CORONARY-ARTERY DISEASE

SIR,—In your leading article of March 22 you quote the statement that "in the healthy organism fibrinolysis is in a dynamic equilibrium with the fibrin-depositing coagulation process", the implication being that so much has been established. This is rather misleading, since what is quoted is an intelligent speculation first put forward to my knowledge by Nolf in 1908, and adopted as a working hypothesis by many workers, including Astrup However attractive the concept may seem it should be made clear that it is unsupported by direct evidence

It will be a pity if the observations of various workers on fibrinolysis in vitro, including the effect of fat, be pressed into speculative dynamic hypotheses subsequently to be quoted as if proven Such a tendency is likely to retard and not to advance knowledge

Gloucester

G R. FEARNLEY

RECTAL METHYLPENTYNOL IN LABOUR

SIR,—The place of methylpentynol in labour is now well recognised, but rectal administration receives no mention This route has been found effective in over 5000 women admitted to the Birmingham Maternity Hospital in the past three years

This method was first tried when it was noted that the patient who most often vomited the oral capsule was the nervous primigravida—the patient whose apprehension it was hoped to relieve, not increase Bourne[7] reported that 8% of patients vomit the capsule, but a second dose is usually retained By use of the rectal route, increase of nervous tension from this vomiting can be avoided without loss of the drug's efficiency

Methylpentynol is given half an hour after an enema to a patient in early established labour The usual dose is 750 mg (i e., 3 capsules), inserted with the finger as far as possible beyond the anal margin. Occasionally in a very nervous primigravida 1 g of methylpentynol is given, and, again uncommonly, the dose may be repeated in not less than three hours When the patient's anxiety is associated with painful contractions it is our practice to give 100 mg of pethidine hydrochloride intramuscularly with the initial dose, for methylpentynol does not relieve pain.

The drug is as efficient when given rectally as it is by mouth. The clinical impression is that labour is shortened and the incidence of postpartum hæmorrhage is not increased

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[3] Cottet, J , Vignalou J Redel J , Colas-Belcour *Bull mém Soc méd Hôp Paris* 1953, 69 903

[4] Mathivat, A., Cottet J *Ibid* p 1030

[5] Cottet, J , Mathivat , A., Redel, J *Pr méd* 1954, 62, 930

[6] Rossi B , Rulli, V *Amer Heart J* 1957, 53, 277

[7] Bourne, G *Lancet*, 1954, i 522

If it is given late in the first stage, pressure of the head during the second stage will at times expel a proportion of the dissolved capsule and drug from the anus As it is a brilliant green it is easily distinguishable from meconium

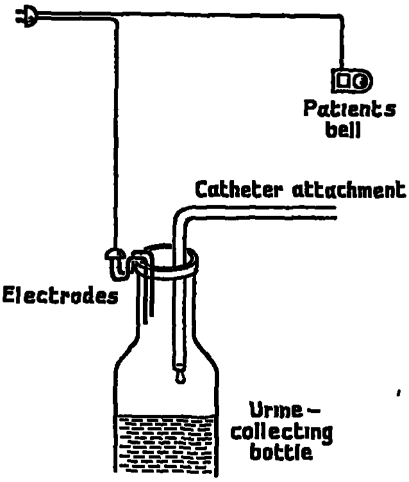
No ill effects have been seen, either generally or locally in the rectum The infant appears unaffected

This method has been of value in general practice, where constant supervision in the early stage of labour is not always possible

University of Birmingham W L **Whitehouse**

AUTOMATIC SIGNAL FOR URINE-COLLECTING BOTTLES

Sir,—It is sometimes hard for nurses, especially during busy night-watches, to cope with the rapidly filling urine-collecting bottles of polyuric patients with indwelling catheters An automatic device for calling the nurses' attention to a full bottle would therefore be of value, and the following signal system was constructed



Two electrodes, connected to the regular patient-bell system (working under 24 volts) are put into the upper part of the urine-collecting bottle (see accompanying figure), as soon as the urine reaches the electrodes, the electric circuit is closed (by electrolysis of the urine), and the bell rings—incessantly, of course, thereby differentiating this call from the normal one-ring call by patients

Our nurses appreciate this device Urine collections are now more accurate, and ward hygiene has improved

I am grateful to Mr J Fraenkel, the hospital electrician, for his advice

Shaarei Zedek General Hospital,
Jerusalem J **Leurer**

NO PEACE FOR THE PATIENT

Sir,—" Ex-Patient " (March 22) lists forty separate calls on her attention during the hospital day, but does not describe how sleep is murdered at night too A recent extended visit to hospital (when I had every reason to be grateful for the excellent care which I received) opened my eyes, both figuratively and in fact

The main causes of the disturbance seem to be the clanging and squeaky trolleys (which are apparently indispensable to nurses in the course of their duty), and the constant shouting of the senile and demented Could not the hospital trolleys be oiled, and the senile all be placed together in one ward? In order to fill a ward, medical and surgical patients might have to go together, but, after all, this is supposed to be an age where barriers are breaking down

While the vast majority of patients do not suffer physically at all under these nocturnal disturbances, the effect on children (and there is usually one in every ward in a large general hospital) must surely be bad

The Medical School,
Manchester Valerie **Frazer**

P A S AND THE PATIENT

Sir,—We should like to join the discussion which has followed our article on outpatient P A S therapy [1–6]

Our main aim was to indicate the *size* of the problem presented by the failure of patients to consume their prescribed P A S Whether the default-rate is 50% (as found by us in the 151 members of a complete outpatient population), or whether it is 25% [7] or 22% [5] (as found in more selected groups), the conclusion must be the same patients who fail to take P A S form a very substantial proportion of those so treated We cannot believe that patients vary so much from district to district that any physician could afford to disregard this fact when deciding to use oral medication The difficulties of providing an alternative to long-term streptomycin and isoniazid [2,5] are freely admitted, but they must be weighed carefully against the possible failure to take P A S The toxic effects of streptomycin, in our experience, can partly be avoided by giving equal parts of streptomycin and dihydrostreptomycin, and this is our practice in patients over 50 years of age If oral therapy is chosen, then every encouragement and explanation must be given to the patients, and urine tested on frequent and unexpected occasions

Our second aim was to draw attention to a modification of the ferric-chloride test which is simple enough to use as a routine in outpatient departments and is, when performed exactly as described, sensitive enough to detect P A S taken in full dosage whilst minimising confusion with the usual doses of aspirin A test that is too sensitive would react strongly with the urine of patients who have taken aspirin or salicylate, inadequate doses of P A S would also give positive results At the same time we consider that the problem of occasional false results is of little importance compared with the default-rate revealed

The detection of calcium B-P A S in the urine is affected by the dosage schedule and dose/test time intervals as indicated by Dr Lauener and Dr Friedrich [6] During the period of our trial the daily prescriptions were 14 g of calcium B-P A S or 10 g of P A S We have felt these to be the minimum desirable doses At this dosage of calcium B-P A S the proposed increase in sensitivity [6] is unnecessary and in fact undesirable in its present form the test may well be negative if patients are taking very low doses of calcium B-P A S, but we feel this to be an advantage We always prescribe oral P A S in two equal daily doses at twelve-hour intervals, as you recommend,[2] and therefore our single dose of calcium B-P A S was always twice that mentioned by your correspondents [6] During our trial calcium B-P A S was prescribed in 43 cases In 21 (49%) a positive urine test was found and in 9 cases the test was still positive at ten to twelve hours after ingestion It thus seems clear that a 7 g dose of calcium B-P A S is capable of giving a positive reaction to our ferric-chloride test, which should be of sufficient sensitivity to be of practical value to those physicians who continue to prescribe this drug We ourselves are not convinced that calcium B-P A S is as effective in preventing isoniazid resistance as is P A S, and for this and other reasons we no longer use it

However, to return to the main argument, even if we assumed that all our negative tests with calcium B-P A S were false (which we do not believe), the proportion of defaulters among our patients is lowered only from 50% to 36% It is evident that all published work on this subject has revealed a high default-rate in taking P A S

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1 Dixon, W M, Stradling, P, Wootton, I D P *Lancet*, 1957, ii, 871
2 *ibid* p 881
3 sp Simon D J *ibid* p 947
4 Edwards J H *ibid* p 1171
5 Leggat, P C *ibid* p 1283
6 Lauener, H, Friedrich, T *ibid* March 15, 1958, p 592
7 Simpson, J McD *Tubercle*, 1956, 37, 333

Whereas, in the case of this drug, the unpleasant side-effects provide an adequate reason, we believe that the issue may be much wider A similar picture might well be revealed in the medication for diseases other than tuberculosis

Finally, may we express our general disapproval of eponyms? In fact I D P W was responsible for the modification of the standard ferric-chloride test, so to call it "Dixon's test" would be doubly wrong

Hammersmith Chest Clinic,
London, W 12

W M DIXON
PETER STRADLING
I D P WOOTTON

A LOW-RESISTANCE RESPIRATORY VALVE

SIR,—I must take exception to the comments of Dr Theron and his colleagues (Feb 22) upon the low-resistance respiratory valve described by my former colleagues[1] It seems that Dr Theron and his colleagues have never seen such a valve, and so their comments on its suitability, however valid, are out of place Furthermore, it is not true to say "The only valve of comparable (sic) resistance is that described ", had they plotted the published resistance of Bannister and Cormack's larger valve in their fig 1, they would have found that it falls between the curves (5a and b) for their own doubtless excellent valve

Oxford

D J C CUNNINGHAM

LUNG RESECTION FOR BRONCHIECTASIS

SIR,—Your annotation of March 22 is a gross misrepresentation of the present position of surgery in bronchiectasis One has come to regard pulmonary resection for localised bronchiectasis as a most rewarding adjunct to treatment in a substantial proportion of cases, and it comes as a rude shock to see you dismiss it as "rarely desirable"

You base your opinion on the grounds of (1) high operative mortality, prohibitive in the case of pneumonectomy, (2) high incidence of morbidity, in particular postoperative collapse, (3) loss of pulmonary function, and (4) extension of bronchiectasis in the residual lung You further state that the results of conservative treatment are favourable

In a personal series of 109 cases, including 17 bilateral cases and 6 pneumonectomies, there were no operative or postoperative deaths One patient died a year after extensive bilateral surgery from pneumonia and respiratory failure About half of the patients were under 20, and all were operated on because of failure of medical treatment There was no case of persistent postoperative atelectasis Only patients who were not symptom-free for a year after surgery were followed up for longer periods, the great majority of patients have been discharged Of the remainder, in no case has further bronchiectasis been shown to develop

Gross localised bronchiectasis (which may include as much as both lower lobes, middle lobe, and lingula) is surely accompanied by loss of function in the diseased areas, and its removal results in little or no further loss of function Pulmonary efficiency may be improved

Finally, you state that no modern advance in technique is likely to affect the most important factor in the alleged failure of surgery—namely, the inevitable distortion of the bronchial tree and interference with the drainage of the remaining bronchi I am aware of no evidence to show that bronchial distortion, if it occurs, is a cause either of bronchiectasis or of impaired bronchial drainage

I submit, Sir, that the figures I have outlined are more in keeping with the experience of a modern chest service than those you quote, and which you admit are unusual in the very high average age of the patients reviewed. It would be a disservice to patients suitable for surgery if they were instead to be condemned to a life of recurrent exacerbations and increasing respiratory disability

Dublin

[illegible]

CLINICAL GERIATRICS

SIR,—Dr Pappworth (March 22) asks in effect whether the clinical signs of any disease differ in elderly as compared with younger patients The answer, I would suggest, is that very often they do, though the differences are greater in those in their 70s and above. To mention but a few: elderly people with pneumonia seldom exhibit any pyrexia, cardiac infarction is common and frequently "silent", and many disorders come to notice only because of mental symptoms which are, however, not evidence of senile dementia It is important that these many differences should be recognised, and the limits of normality at various ages should be better understood

But geriatrics is also concerned with the many ways in which elderly and partially disabled people can be rehabilitated and helped afterwards to live an independent existence outside hospital Those who have not seen this taking place can scarcely believe how many, on being admitted to an active geriatric department, can be made well enough to leave hospital This is achieved not by administration, but by hard work in the clinical field. Should not geriatrics therefore be taught as a branch of medicine by those who practise it, so that we may at last be rid of the attitude of mind which classes patients over 70 as "senile" and thus unworthy of our best attentions?

Ipswich

[illegible]

SIR,—Dr Pappworth does not seem to have read your annotation of March 1, which mentions a number of ways in which the symptoms and signs of disease are modified by age If he consults the current issue of The Practitioner he can read a short paper describing a series of gastric ulcers, proved at necropsy, but not presenting their usual clinical features in old people The same journal also records a group of patients with new growths whose signs and symptoms were cloaked by mental symptoms. The special effects of hæmorrhage in the elderly have been described by Bedford[2], the organic basis of confusional states in the elderly by Flint[3], hypoglycæmia and confusion by Helps[4], and Vince[5] has written on clinical pitfalls in the elderly and so have others elsewhere.

Dr Pappworth mentions an age of 60 for a hypothetical patient This is rather on the young side for a typical geriatric case A survey at Queen's Hospital, Croydon, showed that 34% of the patients were between 80 and 89, while 9% were over 90 The administrative problems, which Dr Pappworth says he can understand, arise because the clinical aspects of disease change as the patient grows older For necropsy proof of this I would refer him to a series of papers in Geriatrics.[6]

Clinical instruction in geriatrics is also desirable because the limits of normality change with age My own book on Old Age was one of the first to give detailed examples of this Holborn and Pemberton have also provided data in *The Health of the Elderly at Home*

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[1] Bannister, R. G , Cormack, R. S *J Physiol* 1954, 124, 4 P

1 *Practitioner* 1957, 178, 233
2. *Lancet* 1956, ii 750
3 *Brit med J* 1956 ii, 1537
4 *Lancet*, 1957, i, 138
5 *ibid* 1955, ii 103
6 *Geriatrics*, 1949, 4 281 *ibid* 1950, 5, 90, *ibid* 1951, 6, 85, *ibid* 195
7, 137, *ibid* 1953, 8, 215, 267

In fact, there is now recorded a considerable body of material dealing with clinical and pathological aspects of disease in old age, which should be brought to the notice of students—the more so since some of their seniors are not familiar with it

London, S W 16 TREVOR H HOWELL

5-BROMOSALICYLHYDROXAMIC ACID FOR TUBERCULOSIS

SIR,—The tuberculostatic action of 5-bromosalicylhydroxamic acid was described by Urbanski and his colleagues [1] More recently Hornung et al [2] have reported that the compound, in a daily dose of 3 g, is as effective as 10 g of *p*-aminosalicylic acid (P A S) in delaying the development of resistance to isoniazid in patients suffering from tuberculosis, They also stated that 5-bromosalicylhydroxamic acid was much better tolerated than P A S It seemed, therefore, that it would be interesting to investigate these claims, and the results of some preliminary experiments may be summarised

In vitro we have confirmed the observations by McIsaac and Williams [3] that high concentrations (of the order of 50 µg per ml) were required to inhibit the growth of *Mycobacterium tuberculosis* On the other hand in vivo, by the mouse corneal method [4] the drug was found to possess some retarding effect on the development of lesions, the order of effectiveness being that of P A S There was no effect on a P A S-resistant strain

Since it is very important to try to find a more palatable substitute for P A S further experimental work is in progress and the question of a clinical trial is under consideration

Guy's Hospital, London, S E 1 J M ROBSON
R KNOX
Brompton Hospital, London, S W 3 R W RIDDELL
Smith & Nephew Research Ltd E M BAVIN

FULMINATING BERIBERI

SIR,—Dr Baron and Mr Oliver write (Feb 15) "admittedly aneurine alone can be successful but deficiency of one vitamin alone is rare" I submit that deficiency of aneurine alone, or rather the need in some individuals for large daily doses of aneurine, is less rare than is generally believed Some authorities state that, except in the initial treatment of acute cardiac beriberi, there is no justification for the administration of single doses in excess of 10 mg [5] [6]

There are reports of isolated instances of the successful use of aneurine in such varying conditions as herpes zoster,[7] varicose ulcers,[8] vesicular atony,[9] and, for its analgesic effect, in the first and second stages of labour [10] I suggest that, if larger doses of aneurine had been used in the past, many more reports of its efficacy in a variety of conditions could have appeared

Three cases are known to me which indicate, not so much a deficiency of the vitamin, as a need for additional daily intake of relatively large amounts

A white man, aged 42, otherwise healthy, had had recurrent attacks of herpes simplex since childhood, these were at times debilitating In 1948 he was given aneurine hydrochloride 200 mg daily by mouth, since that time, except for short periods when the medication was neglected, he has had no recurrences of herpes simplex

A white woman, aged 40, had for several years been taking daily doses of up to gr 15 of cascara sagrada for constipation In 1954 she was given aneurine hydrochloride, and since that time has been taking daily oral doses of 200–400 mg, with complete relief from all symptoms of constipation

A white girl, aged 14, had had nocturnal enuresis since infancy She had been examined, at different times, by a general practitioner, a pædiatrician, a urologist, and a psychiatrist, in each case except for the nocturnal enuresis the child appeared to be normal and healthy No cause could be found for the condition and no medication helped until, in November, 1957, she started taking aneurine hydrochloride Initially she was given 25 mg daily by mouth with partial success, the dose was increased to 400 mg daily by Dec 7, 1957, and maintained at that level since The nocturnal enuresis ceased on Dec 8, and has recurred only once since, when the aneurine was omitted

There is, I submit, often a case for giving aneurine, providing the dosage is high enough Most of the difficulties reported with administration of aneurine, and there have been several,[6] [11] have been during parenteral use, I have not come across a single adverse reaction to oral administration

A thorough study of the need for aneurine in man and its utilisation could be most rewarding

Saint John, New Brunswick JOHN E WASSON

THE LAW AND STERILISATION

SIR,—Your review (March 22) of my book, *The Sanctity of Life and the Criminal Law*, leaves room for misunderstanding which I should be glad of the opportunity to remove You say "Dr Williams' apparent advocacy of compulsory sterilisation might be harmfully taken much further by others than he himself intended" In fact I am not in favour of compulsory sterilisation I merely urged the implementation of the Brock report, which was concerned with voluntary sterilisation

My discussion of the committee's report proceeded as follows (p 108)

> "The committee, which gave attention to this problem of consent, expressed itself as convinced that when the higher-grade defectives ask for sterilisation, perhaps to assist themselves in obtaining a discharge, or in some cases to be allowed to marry, they understand what they ask for 'The essence of a voluntary system,' said the committee, '*is that* those who object should be free to do so What matters is that there should be no compulsion So long as there is no unfair pressure and no patient *is* forced or bribed to consent, it seems to us mere casuistry to discuss how far the patient full appreciates all the implications of consent'"

The terrible abuses of the Nazis did great harm to the cause of eugenics, but in my study of the working of the American sterilisation laws I think I showed that their results gave ground for confidence To quote my own words again

> "The American experience is of great interest because it shows how remote from reality in a democratic community is the fear—frequently voiced by Americans themselves—that voluntary sterilization may be the 'thin end of the wedge', leading to a large-scale violation of human rights as happened in Nazi Germany In fact, the American experience is the precise opposite—starting with compulsory sterilization, administrative practice has come to put the operation on a voluntary footing"

And again "No one with experience of sterilisation laws now advocates a compulsory system"

Trumpington,
Cambs GLANVILLE WILLIAMS

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1 Urbanski, T, Hornung, S, Slopek, S, Venulet, J *Nature, Lond* 1952, 170, 753
2 Hornung, S, Amazowicz, F, Broda, Z, Necius-Szczerbinski, Z Paryski, E, Polonczyk, M, Raff, T *Brit J Tuberc* 1958, 52, 19
3 McIsaac, W M, Williams, R T *Biochem J* 1957, 66, 369
4 Rees, R J W, Robson, J M *Brit J Pharmacol* 1950, 5, 77
5 British Pharmaceutical Codex, p 50 London, 1954
6 Martindale, W The Extra Pharmacopœia, vol I, p 175 London, 1952.
7 Waldman, S, Pelner, L *Amer Prof Pharm* 1948, 14, 1134
8 Oschner, A, Smith, M C *J Amer med Ass* 1940, 114, 947
9 Roome, N W *Canad med Ass J* 1946, 54, 151
10 Dubiau, J H, et al. *Abstr World Surg* 1948, 4, 46 Quoted by Martindale W The Extra Pharmacopœia, vol I, p 177 London, 1952
11 Leitner, Z A *Lancet*, 1943, ii, 474

MEDICAL SUPERVISION IN TREATMENT OF OBESITY

SIR,—Obesity is now one of the leading causes of death and disability,[1] and its cost to the nation is incalculable Yet it has been proved beyond doubt that sufficient reduction of calorie intake will produce loss of weight in every case

A survey of 500 consecutive patients seen in the medical outpatient department at St James' Hospital, Balham showed that about a third had conditions either produced or exacerbated by obesity—defined as a weight more than 20% above normal weight for height and age according to the standard tables of Kemsley [2]

Before July, 1956, some of these patients were given dietetic instruction and referred back to their own doctors; others, usually those with more serious medical conditions, were treated for a time in the outpatient department, often seeing a different doctor each time, and when weight-loss seemed satisfactory, they were discharged with instructions to continue on their own

A follow-up of 133 of these patients after at least six months showed that weight-loss had been satisfactory (i e, more than 30% of excess weight had been lost) in only 6% 63% had failed to lose more than 7 lb, and 26% had actually gained weight

During the past eighteen months an attempt has been made to treat obesity more vigorously No patient has been discharged until the weight has been normal for at least six months I saw all the patients myself, most of them at every attendance, time has been spent in discovering the background of each patient's obesity and the special difficulties in treating it.

Treatment was dietary whenever possible, with the object of re-educating the patient's appetite rather than achieving a rapid weight-loss The principles of low-carbohydrate diet were explained Drugs, including dexamphetamine sulphate, 'Preludin', 'Drinamyl', and thyroid extract were used when they were considered necessary Patients were seen initially at intervals of two, three, or four weeks, and when weight-loss was satisfactory the intervals between appointments were gradually extended to three or six months

SUCCESS IN THE TREATMENT OF OBESITY

—	Old methods (133 patients)	New methods* (120 patients)
Satisfactory weight-loss (more than 30% of excess weight lost)	6%	67%
Slight weight-loss (more than 7 lb but less than 30% excess weight)	31%	27%
Unsatisfactory weight-loss (less than 7 lb or gain in weight)	63%	6%
Reached and maintained normal weight	4%	25%*
Gained weight during treatment	26%	1 7%

* Ultimate figures will probably be higher since most of these patients are still under treatment.

Of 120 patients who have attended for more than three months, 67% have achieved satisfactory weight-loss and 25% have already reached and maintained normal weight. Only 6% have failed to lose at least 7 lb, and of these 1 7% have gained weight Results in the previous "failures" were as good as in the new cases

The results in the two groups are compared in the accompanying table, and indicate that the treatment of obesity without strict medical supervision is unsatisfactory, whereas close medical supervision results in successful weight-loss in a high proportion of cases The improvement in health in these patients, many of whom have been semi-invalids for years, is enormous Many have previously cost the hospital many hundreds of pounds, but their health is now so much improved that they no longer require frequent attendances and investigations in various departments of the hospital It seems likely that if every obese patient seen either in hospital or in general practice was treated along these simple lines, the health of the nation would be improved and the cost of the National Health Service reduced

I thank Dr Alexander Kahan, consultant physician at St. James' Hospital, Balham, for permission to study his patients, and for his helpful advice and criticism

St. James' Hospital,
London, S W 12.

A. G MULLINS

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1 Marks, H H *Hum Biol* 1956, 28 217
2 Kemsley, W F F *Ann Eugen* 1952, 16, 316

ALLERGY TO COW'S MILK

SIR,—As the leaders commercially of the present trend towards evaporated milk as a standard infant food in Great Britain, we must comment on the final paragraph of your annotation of Feb 8 in which you suggest that the dried milks used in this country are less liable than evaporated milk to give rise to allergy

While we assess—from constant contact with doctors—that milk allergy is fairly frequent, we have on record, from the same group of professional contacts, an extremely dramatic improvement in, particularly, eczematous conditions when the children were changed from dried-milk foods to evaporated milk

This is supported by Sturrock [1] in a study of four groups of infants fed on breast milk (control), cow's milk, dried milk, and evaporated milk Breast milk and evaporated milk showed up to advantage 60% in both these groups had a clear skin at each of the six weekly observations made. Cow's milk and National dried milk showed up unfavourably on the whole and, from clinical experience generally, it was not surprising to find the relatively high incidence of urticaria in babies taking these milks

Ratner and Gruehl [2] said that evaporated, freshly boiled, and acidified evaporated milk, fed by mouth, was notably less sensitising They also refer to feeding experiments with various forms of milk undertaken to determine whether there was a further diminution of sensitisation when heated milks were fed. Raw skimmed milk, 'Smaco' 303 (special hypo-allergenic preparation), and dried milks sensitised more than 50% of the animals, while milk freshly boiled for four hours was much less liable to produce sensitisation, and so was evaporated milk.

Ratner [3] had this to say of dried milks

> "The antigenic changes that result from various drying processes applied to milks were studied, and it was found that the rapid drying—which is almost instantaneous—did not influence or diminish the antigenic powers of the milk proteins "

We believe that the production of special hypoallergenic milk powders both in this country and the United States indicates the awareness of dried-milk manufacturers that normal milk products have shortcomings for some milk-sensitive infants

Evaporated milks, under exhaustive research in the United States, have clear hypoallergenic advantage over other cow's milk preparations (including dried milks), with the possible exception of fresh cow's milk boiled for four hours

We note with interest your reference to the desirability of a British study of the incidence of milk-protein allergy, and we hope that such research will in fact be undertaken

General Milk Products Ltd.,
London, W C.2.

R. H WOODCOCK
Manager, Medical Department.

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1 Sturrock, M *Med Off*, 1952, 87 143
2 Ratner, B, Gruehl H L *Amer J Dis Child* 1935, 49, 287
3 Ratner B *J Amer med Ass* 1935, 105, 934

Obituary

ALEXANDER JAMES HUTCHISON RUSSELL

Kt, C B E, M A, M D, LL D St And, D T M, D P H

Sir Alexander Russell, whose death on March 22 we announced last week, had a distinguished career in India, where he was public health commissioner from 1933 until he entered his busy retirement in 1939

He was born in 1882, the son of Walter Nicoll Russell, a schoolmaster in Glen Devon, and he was educated at Dollar Academy and the University of St Andrews, where he graduated M B in 1906 The following year he joined the Indian Medical Service After a period of military duty he was appointed for civil employment to the Madras Presidency and in 1913 he became medical officer of health of Madras city Before long he realised that his chief interest lay in preventive medicine, and in 1914 he was appointed professor of hygiene and bacteriology at Madras Medical College After five years he turned to pathology and he held that chair for several years

In 1921 Russell re-entered the public service as provincial director of public health He was selected as medical assessor to the Royal Commission on Labour in India, which was set up in 1930, and in 1931 he was a delegate to the Office International d'Hygiène in Paris While he was in Madras he reorganised the public-health department and trained a body of keen and devoted young medical officers, inspiring them with his own high ideals of service With his appointment in 1933 as deputy director-general of the I M S Russell reached the most exacting phase of his career In the same year he was made public health commissioner with the Government of India, and held this post till 1939 His reports were first-rate examples of his power of shrewd analysis and terse, vigorous expression, and his editions of *McNally's Sanitary Handbook of India* (1916 and 1923) were widely read

Of Russell's work in India E W C B writes

Long before he became public health commissioner he had shown, during his career in Madras, high administrative ability, and though he succeeded to the appointment during a period of financial stringency his drive and enthusiasm overcame many difficulties As in Madras his tenure was one of steady progress towards the building up of a sound public-health conscience in the Government of India He was an expert in statistics, having held a fellowship under the Rockefeller Foundation and studied the subject in the United States As a man Russell was a sturdy, lovable Scot, intensely loyal to all his officers, and to his chiefs in the Medical Service At headquarters in Delhi and Simla his administrative qualities found full scope and his opinion, never intolerant, was invaluable India owes a great debt to Russell and the I M S salutes one of their worthiest officers

Soon after Russell returned to this country in 1939 war broke out He began his nominal retirement by helping the group officer of the Emergency Medical Service at Oxford, and during the winter of 1939–40 he lectured on hygiene to the senior medical students In June, 1940, he joined the Department of Health for Scotland as a temporary medical officer and a few months later was appointed to the temporary post of deputy chief medical officer in the same department, with special charge of the national campaign against diphtheria, and he held this post till 1945 During 1944 his services were asked for by the Colonial Office as chairman of a committee to report on the medical and health services of Trinidad and Tobago, and in 1945 he visited Austria as a member of a medical mission on epidemic control

J M M writes

In this active third phase of his career he added distinction to his wide reputation, by devoted and unselfish service He was admired and loved for his delightful personality, he brightened all social relationships with his pawky humour, and shared in all the activities of his colleagues He had been in his regimental polo team in the early days, and in his later years he played a steady game of golf and was a member of the Royal and Ancient Even in his final retirement at Bridge-of-Allan he took his place on many local committees, while he and his wife gave hospitality in generous measure It was a happy time so close to the hills that watch over Glen Devon

RALPH EWART JONES

B Sc Birm, M R C S, D P H

Dr Ewart Jones, director of the regional public health laboratory at Coventry, died on Feb 8 at the age of 53

He was born at Sutton Coldfield and educated in Birmingham at King Edward's School and at the medical school After qualifying in 1927 he held a house-appointment at Hallam Hospital, West Bromwich, and was assistant clinical pathologist at Birmingham General Hospital before he became assistant to Prof J F D Shrewsbury in the department of bacteriology of Birmingham University Later he was appointed senior lecturer in the department During the late war he was seconded to the Emergency Public Health Laboratory Service under the Medical Research Council, and he was in charge of a laboratory at Wrekin College, Wellington, which was ultimately transferred to Hereford In 1948 he was appointed to his present post and for the past two years he had also been honorary lecturer in bacteriology in the University of Birmingham He leaves a widow

P M P writes

I became Ewart Jones' assistant at a time when he had every appearance of robust health, and came to value him highly as a director, a bacteriologist, and a friend He was conscientious and painstaking, a man of charming personality who gave and expected the best at all times The welcome he gave in his home was without reservation, and behind his urbanity was always a quiet humour which was a delight to those who knew him That he possessed the sterner qualities of supreme courage and impassive fortitude became evident when illness overcame him, for his demeanour remained calm and unflinching, and he did not alter his way of life

Parliament

Consultants

Mr KENNETH ROBINSON asked the Minister of Health the number of consultants, excluding psychiatrists, in the employ of each regional board and the number of staffed beds, excluding mental and mental-deficiency beds, in and the population served by each region —Mr DEREK WALKER-SMITH replied The information is as follows

Regional hospital board	Number of consultants, whole-time and part time (excluding psychiatrists) at 31 12 56	Number of staffed beds (excluding beds allocated to mental illness and mental deficiency) at 31 12 56	Estimated population of region in thousands at 30 6 56
Newcastle	353	15,338	2914
Leeds	299	17,753	3066
Sheffield	357	19 716	4230
East Anglian	167	7254	1485
N W Metropolitan	642	17,930	3942
N E Metropolitan	531	18,966	3103
S E Metropolitan	556	19,933	3229
S W Metropolitan	703	25,216	4707
Oxford	188	7133	1503
S Western	330	16,621	2792
Welsh	293	15,494	2608
Birmingham	491	23,047	4547
Manchester	409	23,611	4381
Liverpool	276	14 180	2130
Total	5595	212,492	41 667

Notes and News

ANOTHER "UNIVERSAL DIAGNOSTIC TEST"?

LAST month there was quite a flutter in some American newspapers about the announcement of a "new test for the early diagnosis of disease" "Blood Cell Study Seen Quick Way to Diagnose All Disease Medical Break-Through?" was the headline in the *Baltimore News-Post* for March 19 Prof Winston H Price, of Johns Hopkins University School of Public Health, who is in charge of the team working on these tests, and had described his work at a closed meeting, refused to be drawn by reporters, but on March 23 the *New York Times* gave a sober and informative account of this work

Apparently Dr Price and his colleagues have been working on the serum-mucoproteins These substances have been studied for many years, as long ago as 1940 Rimington described their characteristic properties[1], and ten years ago Winzler et al[2] showed that the serum-mucoprotein was a mixture of three components It has long been known that the serum-mucoproteins are increased in rheumatoid arthritis and in other diseases too, thus Kelley et al,[3] for example, found that results from estimating the serum-mucoproteins roughly paralleled changes in the erythrocyte-sedimentation rate, except that in chronic heart-disease the mucoprotein estimation was the more reliable The changes in serum-mucoproteins have been accepted as one of the non-specific manifestations of diseases involving tissue destruction—like the erythrocyte-sedimentation rate and C-reactive protein What Dr Price and his colleagues are reported to have found is that the relation to each other of the three serum-mucoprotein components differs in different diseases, and that completely abnormal mucoproteins appear in some conditions Thus, according to the *New York Times* report, in nephrosis and nephritis only one of the three normal mucoproteins was present, the other two being missing altogether, and in mental diseases all the serum-mucoproteins were abnormal In cancer at four sites—prostate, kidney, gastrointestinal tract, and lung—four abnormal mucoproteins were present, the proportions of these four abnormal components was the same for tumours at the first three sites but differed for "lung" cancer In acute diseases, such as rheumatic fever, the serum-mucoprotein values were high and remained raised after clinical recovery

An announcement from Johns Hopkins, quoted by the *New York Times*, is properly cautious "It cannot be too strongly emphasized", it states, "that the number of cases in each disease that have been analyzed is small, and that much more data will have to be accumulated before the true significance of these patterns (of the blood-serum fraction) can be determined." But it seems from this report that Prof Winston Price has extended the study of serum-mucoproteins to a point where he hopes that the results will give more specific information than has previously been obtainable from tests of this type All physicians are familiar with the patient who has vague symptoms and is found to have a raised erythrocyte-sedimentation rate, such a finding inevitably leads to further and often fruitless blood-counts, X-rays, and studies of blood chemistry The serum-mucoprotein fractionation may indicate more specifically where to look, and whether to seek infection or malignancy From the preliminary results quoted, the pointer to the site of a lesion is hardly specific, but the indication about the type of lesion may be more reliable Work on the early detection of malignancy by studying changes in serum-proteins has been going on for a long time Perhaps the Johns Hopkins group have really made the method work There is no denying that such a test would be very useful

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[1] Rimington, C. *Biochem J* 1940 34, 931
[2] Winzler R J Devor, A W, Mell J W, Smyth, I M *J clin Invest* 1948 27 609
[3] Kelly, V C., Adams, F H., Good, R A *Pediatrics*, 1953, 12, 607

INTERNATIONAL CHILDREN'S CENTRE

AT the opening ceremony in 1950, Prof Robert Debre said "Conceived as an institution for information, instruction, mutual aid and cooperation, the International Children's Centre hopes to contribute to better conditions for all the children of the world" Last year the activities of the centre included two seminars (on primary tuberculosis and pertussis), research on tuberculosis vaccination, the prevention of rheumatic fever, and the growth and development of children, and eight courses of instruction on such topics as reablement of crippled children, school health, child welfare (including a five-month course for African midwives at Dakar), and the care of premature infants This and other work is set out in the annual report.[1]

HEALTH SERVICES FOR THE ARAB REFUGEES

ONE of the most tragic results of the 1948 war in Palestine has been the plight of the several hundred thousand Arabs who then left their homes to take refuge in neighbouring Jordan, Lebanon, Syria, and the Gaza Strip Today most of these people still live in the same places where in 1948 they arrived hungry and destitute awaiting relief from the local Arab Governments

As the weeks following their exodus stretched into months, and they found that they could not return to their homes, it became apparent that more organised relief was essential if a major catastrophe was to be avoided The risk of epidemics was already serious when in 1949 the United Nations Relief for Palestine Refugees was set up to carry out relief with the aid of the international committee of the Red Cross, the League of the Red Cross Societies, and the American Friends Service Committee

The small health teams which were organised a decade ago by a W H O specialist to meet the emergency have since developed into an efficient health force serving nearly a million refugees now living in camps, towns, and villages scattered over 100,000 square miles in four different countries The United Nations Relief and Works Agency which took over relief activities in 1950 is now spending at the rate of $5 million a year on its health programme alone. Its 3500 employees include 120 doctors and dentists and over 450 nurses, nursing auxiliaries, and midwives Its technical direction is the responsibility of the World Health Organisation There are 92 clinics (attracting 6 million visits a year) and 2000 hospital beds in U N R W A and other hospitals, but preventive work is given priority it includes attention to water-supplies and disposal of sewage and waste, an anti-malaria campaign (with swamp drainage and insecticide spraying), which has led to a fall in the proportion of malaria patients seen in the clinics in East Jordan from 18 5% in 1953 to 0 66% last December, mass inoculations (including, last year, 254,000 against typhoid and 497,000 against smallpox), supplementary feeding of the sick, of pregnant and nursing women, and of children, and health education, particularly in hygiene and child care At the maternal health centres, besides receiving such instruction, pregnant women (100,000 consultations last year) are cared for, including tests—and, where necessary, treatment—for syphilis, the provision of a simple layette, and supervision of the infants up to the age of two years

By these means serious epidemics have been avoided, and in some ways, the health of the refugees has been improved, but their housing is far from satisfactory and their rations are the minimum needed for subsistence The work of the health programme must continue, and so must the contributions of Governments to the funds of the agency

BETHLEM AND MAUDSLEY HOSPITAL REPORT

IN his article of March 15 (p 578) Dr C P Blacker referred to the triennial statistical report of the Bethlem Royal Hospital and the Maudsley Hospital for the years 1952–54, which he has edited The report has now been published (pp 152, 10*s* 6*d*)

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[1] Berthet E Report for 1957 of the International Children's Centre Château de Longchamp, Paris, 16^e

CORTICOTROPHIN—A CORRECTION

LAST week we said that corticotrophin preparations may now be prescribed on form E C 10 This is not so

LESS DIAMORPHINE USED

SOME time ago the Economic and Social Council of the United Nations expressed the hope that diamorphine (heroin) would no longer be used[1] In its eighth report[2] the W H O Expert Committee on Addiction-producing Drugs notes " that the relatively small residuum of licit use of diacetylmorphine was tending to be further reduced " The committee believes that this substance " can be replaced by more than one drug with less risk to public health "

University of Dublin

On Thursday, May 1, at 5 P M , at Trinity College, Dublin, Prof A Hagedoorn, of Amsterdam, will give the Montgomery lecture on the gross and minute defects of the germ cells and clinical ophthalmology

Royal College of Physicians of London

On Tuesday and Thursday, April 15 and 17, Dr J St C Elkington will give the Lumleian lectures on cerebral vascular disease in the light of modern techniques

On Tuesday and Thursday, May 13 and 15, Dr Paul Wood will give the Croonian lectures His subject will be the Eisenmenger syndrome, or pulmonary hypertension with reversed central shunt All the lectures will be given at the college, Pall Mall East, S W 1, at 5 P M

St George's Hospital Medical School, London

Postgraduate demonstrations in psychiatry will be held at the School, Hyde Park Corner, S W 1, on alternate Thursdays at 5 P M They are open without fee to doctors and senior medical students The first will be given by Sir Paul Mallinson on April 17

West London Medico-Chirurgical Society

On Wednesday, April 16, at 8 30 P M at the house of the Royal Society of Arts, John Adam Street, W C 2, Sir Gordon Gordon-Taylor will give the Cavendish lecture His subject will be On Tradition

Nutrition and Climatic Stress

The Scottish group of the Nutrition Society is holding a symposium on this subject at the Hannah Dairy Research Institute, Kirkhill, Ayr, on Saturday, April 26 Papers will be read on human and animal nutrition Further particulars may be had from Dr J Davidson, The Rowett Research Institute, Bucksburn, Aberdeenshire

International Congress for Manipulative Therapy

This congress will be held in Baden, Switzerland, from May 1 to 4 The speakers will include Dr J H Cyriax and Dr Alan Stoddard Further particulars may be had from the president, Dr J C Terrier, Badstrasse 64, Baden, Switzerland

N H S Award

The Industrial Court has awarded a 4½% pay increase to more than 1100 technical staff in the National Health Service The staff who will receive the increase will include medical photographers, dark-room technicians, and physics technicians They received their last increase in August and September, 1956 The new rates will be paid from the beginning of March

Laboratory Animals Centre

This centre is holding a symposium on Monday, May 5, at 9 30 A M, at 1, Wimpole Street, London, W 1, on the organisation and administration of an animal division Further particulars may be had from the Laboratory Animals Bureau at the centre's new address at the M R C Laboratories, Woodmansterne Road, Carshalton, Surrey

The high sheriff of Carnarvonshire for 1958-59 is Prof R H Parry, formerly principal medical officer to Bristol City Council

Dr George E Wakerlin has been appointed medical director of the American Heart Association, in succession to Dr Eugene B Ferris, who died last September Dr Wakerlin, formerly professor of physiology and pharmacology at the University of Illinois, took up his duties on April 1

Dr Richard Emanuel is to be one of the recipients of an award made by the American Society for Clinical Investigation for work carried out at Vanderbilt University, Nashville, on indicator dilution methods for describing circulatory systems He was given a year's leave from the National Heart Hospital, London, to take part in this investigation

The United Hospitals' Choir is to give a performance of *Belshazzar* by Handel at 7 30 P M on Tuesday, April 22, at St James's and St Peter's Church, Piccadilly, London, W 1 Admission will be by programme (*3s 6d*, *5s*, and *7s 6d*), which may be had from Miss J Magrath, 18, West Side, Clapham Common, S W 4

The photographic department of St Mary's Hospital Medical School, London, W 2, has made 15 films, which may be borrowed free (except for a few shillings for postage and packing) for medical audiences (including nurses) or scientific film societies All are 16 mm A catalogue may be had from the department

The Directory of Child Guidance Services in England and England and Wales, published by the National Association for Mental Health, lists alphabetically under counties the child-guidance clinics and gives for each the address, names of staff, and days of attendance. Copies (*5s*) may be had from the Association, 39, Queen Anne Street, London, W 1

To any doctor who writes for it the National *Marriage* Guidance Council will send a free copy of *Sex in Marriage*, to which we referred on March 1 (p 487) Requests should go to Mrs Angela Reed, publications officer, National *Marriage* Guidance Council, 78, Duke Street, London, W 1, who will also supply order forms which can be given to patients wishing to order their own copies direct from the Council

Diary of the Week

APRIL 6 TO 12

Tuesday, 8th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln s Inn Fields, W C 2
5 15 P M Mr E G Muir Carcinoma of the Rectum and Anterior Resection
6 30 P M Mr T Holmes Sellors Diagnosis and Treatment of Atrial and Septal Defects
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
8 P M *Psychiatry* Dr Bernard Zeitlyn Postoperative Psychoses

Wednesday, 9th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 15 P M Mr F W Holdsworth Traumatic Paraplegia
6 30 P M Dr R A Shooter Spread of Infection in Hospitals
ROYAL SOCIETY OF MEDICINE
4 30 P M *Physical Medicine* Dr C D Calnan, Dr Stephen Mattingly, Dr Verna Wright Psoriasis and Arthritis

Thursday, 10th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 15 P M Mr D N Ross Hypothermia as an Aid to Surgery
6 30 P M Mr Rainsford Mowlem Treatment of Lymphœdema

Friday, 11th

ROYAL SOCIETY OF MEDICINE
5 30 P M *Anæsthetics* Dr George Edwards John Snow s London Associations Dr M H Armstrong Davison John Snow and the Enlightenment.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330 Gray s Inn Road, W C 1
3.30 P M Mr C. Gill-Carey Earache—the Differential Diagnosis

Appointments

BRODIE, JAMES, M D St And , D P H consultant bacteriologist to take charge of the laboratory, City Hospital, Aberdeen

FOSTER, D W , M B , B SC Wales, D P H M O , Pontypridd, Glamorgan

KINGSLEY PILLERS, ELIZABETH M , M D Cantab , D M R assistant radiotherapist, Addenbrooke's Hospital, Cambridge

O HARE, BERNARD, M B N U I , D M R D consultant radiologist Derby no 1 H M C and Burton-on-Trent H M C

PETRIE, W O , M B E , M B Edin , D P H , D T M & H assistant M O H , Berwickshire

SEFTON, ELIZABETH M , M R C S , D C H , D P H senior M O (maternal and child welfare), Gloucestershire

WRIGHT, E W , M B Edin , D P H deputy M O H and deputy principal school M O Bournemouth

YARWOOD, G R , M B Birm , F R C S consultant surgeon, Birmingham (Dudley Road) H M C

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[1] *Lancet* 1955, i, 1311

[2] *Wld Hlth Org tech Rep Ser* 1958 no 142 Pp 12 1s *9d* Obtainable from H M Stationery Office, P O Box 569, London, S E 1

The Lancet · Saturday 12 April 1958

THE THYROID NODULE*

SELWYN TAYLOR†
M Ch Oxon, F.R.C.S
SURGEON, KING'S COLLEGE HOSPITAL; LECTURER IN SURGERY, POSTGRADUATE MEDICAL SCHOOL OF LONDON

IT is almost twenty-five years since, as a physiology student, I read Harrington's (1933) textbook on the thyroid gland, yet on rereading my notes I find little that needs altering after all the intensive research work lavished on this single endocrine gland in the succeeding quarter of a century There is much, however, to add to this earlier account, and here I want to weave together something old and something new to try and explain why nodules appear in the thyroid gland, their natural history, and how we may hope to diagnose them correctly and treat them rationally Those of us who still like to be called general surgeons are continually confronted by the patient who harbours a readily palpable thyroid nodule, and our first question must surely be is this goitre simple, toxic, or malignant? I have a particular interest in simple or non-toxic ones, certainly they are the most common

The Simple Nodule

Lack of Iodine

Simple goitre is primarily due to failure of the thyroid gland to obtain sufficient iodine to maintain its normal structure and function In most parts of the world a deficiency of iodine is the commonest cause of a nodule in the thyroid gland of a young person and of multiple nodules in older people The ancients used burnt sponge and seaweed to treat goitre, which was splendid empiricism because iodine was not discovered until 1811 by the Frenchman Courtois (1813) At that time our fleet was blockading the French coast, and Napoleon could not import the nitrates he required to make gunpowder His backroom boys therefore devised other means of obtaining nitrates, they used a process involving, at one stage, the admixture of seaweed ash with sulphuric acid in metal vats It seems that Courtois one day had perhaps added stronger acid than usual, because beautiful violet vapours were seen to arise which proved to be a new element, iodine Thus Napoleon's gunpowder gave us iodine, just as nuclear fission has given us radioactive iodine

Soon after Courtois' discovery of the new element Sir Humphry Davy (1814) confirmed the presence of iodine in seaweed and Fyfe (1819) in sponges, and as early as 1816 Dr William Prout was prescribing potassium iodide for goitre Some remarkable micro-assays by Chatin (1850–76) put the whole subject on a sound scientific foundation, from which it was unfortunately toppled by some unsatisfactory attempts at preventing goitre with iodine in the French provinces Thus the way was paved for the infective theory of goitre to gain the ascendant, probably helped by the great interest taken at that time in the work of Pasteur and Koch However, although this temporarily distracted attention from a low intake of iodine as the cause of thyroid enlargement, it encouraged investigations into those other goitrogenic substances whose presence becomes important in the iodine-deficient areas of the world In such areas the daily intake of iodine is less than 100 µg, the quantity determined by Curtis and Fertman (1950) as necessary for normal function of the thyroid gland in an adult

Evolution of Simple Goitre

The natural history of thyroid enlargement in an area of endemic goitre has been carefully documented in the past (Olesen 1924, 1926, 1929, Olesen and Taylor 1926, 1927), especially by public-health workers In an area of average severity the thyroid appears moderately enlarged in early childhood This type of enlargement was called by Murray et al (1948) the Rossetti neck At the age of 5 years, about a quarter of the boys and a third of the girls may be so affected, and by puberty the incidence is usually at its highest

Puberty goitre has been regarded as a physiological (McCarrison 1917) rather than a pathological response to lack of iodine because it reflects the great demands made on the gland at this period and may be entirely reversible I have, however, seen young adults with thyroid nodules who had only spent the first 5–10 years of their lives in an endemic goitre area and had then moved to a district where the intake of iodine was adequate

After puberty it is usual for the enlarged thyroid gland to diminish in the male but to persist in the female, in whom it usually enlarges a little before each menstrual period and considerably during pregnancy At the age of 30 nodules have often appeared, and the real problem there is when and why the diffuse hyperplasia of puberty becomes nodular in the third decade and later

Autoradiographic Studies

In an attempt to gain insight into the processes taking place in nodular goitre we have prepared in the laboratory autoradiographs from well over a hundred patients operated on for simple goitre

Autoradiography, a technique to which I was first introduced by Brown Dobyns, is ideally suited to the study of goitre because it gives a physiological rather than an anatomical picture of what is going on when the tissues are removed It consists in exposing a slice of the thyroid gland to a piece of photographic film, which becomes black where the tissues contain radioactive material Thus it makes possible a comparison of the histology of any area with its capacity to concentrate and bind iodine to protein—in other words, to manufacture thyroid hormone

The patients investigated were representative of most types of simple goitre, being drawn from those with sporadic goitre in London and others from endemic areas in Southern Ireland who had come to work in London

Each patient was admitted to hospital and, after a thorough history had been obtained, including details of dietary habits, district where born and bred, and any family incidence of goitre, was given a tracer dose of radioactive iodine The urine was collected for forty-eight hours and the overall activity of the gland determined by the method of Fraser et al (1953) Partial thyroidectomy was done, and slices of tissue were cut through whole lobes to get a good overall picture The tissue was fixed and cut exactly as for ordinary histology, and these giant slices were then put in contact with pieces of X-ray film, which were developed at one, two, and eight days and then compared with the histological sections

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* From a lecture delivered to the section of surgery of the Manchester Medical Society on Dec 10, 1957

† In receipt of a grant from the British Empire Cancer Campaign some of the work described here was done with a grant from the Medical Research Council

Examination of these autoradiographs at once revealed many interesting features In diffuse simple goitre the blackening showed a fairly uniform peppering throughout the gland, but in older patients the greater part of the thyroid gland appeared to concentrate no radioactive iodine at all, there being only small discrete foci of blackening Blackening only takes place in areas where there is iodine-containing colloid Colloid does not necessarily contain iodine The features which distinguished those follicles capable of doing this from the others was that the former were small in diameter, with tall cells Rawson and Starr (1938) showed that increased height of the follicle cells indicated increased stimulation of the thyroid gland In addition these small active follicles were grouped together in a characteristic way The diameters of 100 follicles in active and non-active areas were measured in two axes at right-angles to each other The diameters of the active follicles were not only about a third of those of the inactive ones but also were much more uniform in size (Taylor 1952)

When autoradiographs of the whole series of goitres were examined in conjunction with the histological preparations and case-histories of the patients, it appeared possible to reconstruct the natural history of the disease (Taylor 1953) This evolution of nodular goitre I have divided arbitrarily into five stages, although appreciating that other workers might interpret the results differently

Stage I is diffuse enlargement of the thyroid gland, which shows increased vascularity, a large uptake of radioiodine, and uniform blackening of the autoradiograph This is the typical puberty goitre but may persist for years

Stage II comprises all those thyroid glands which show discrete focal areas of hyperplasia with corresponding blackening of the autoradiograph There are very few patients in whom all the functioning thyroid tissue is concentrated in a single area, Rawson when shown autoradiographs of this condition, immediately described it very aptly as a toxic nodule in a non-toxic gland It is fashionable at present to call this a hot nodule in a cold gland, but it must not be forgotten that the patient presents the picture of normal thyroid (euthyroid) function

Stage III—Before the next stage in this evolution is described, it is necessary to appreciate the internal architecture of the thyroid gland The building-blocks from which the gland is constructed are follicles, each being a spherical structure made up of a single layer of cells covered by a basement membrane and a rich network of blood-vessels Johnson (1953, 1954), by perfusing excised glands with warm saline solution, has split up the connective-tissue planes to show that each 20–40 follicles are bound lightly together to form a lobule, each lobule being supplied by a single artery This important lobular or " unit " construction was known a century ago but in recent years was doubted, probably because of methods of wax-model reconstruction (Rienhoff 1930) from serial sections which hinted at a branching structure

It appears from our autoradiographs that these lobules work as single units and become increasingly more hyperplastic and vascular This stage is typified by disruption with hæmorrhage, which is followed by necrosis, and on the autoradiograph only a rind of active tissue is seen

Stage IV is the end-result of stage III The nodule undergoes resolution in one of two ways either a large lake of colloid fills it and this is found to be free of iodine, or a mass of new follicles grows to supersede it, and again their colloid does not take up radioiodine

Stage V is the multinodular or pudding-stone goitre, brought about by the continued repetition of the process described above, with the result that most of the nodules are inactive and incapable of metabolising iodine, but among them will be found a few active foci which are currently supplying the body's hormone requirements

Experimental Goitre

Nature has made some vast experiments in the production of goitre in various parts of the world, and this has stimulated research, such as McCarrison's in the foothills of the Himalayas fifty years ago and Stanbury's (1954) in Argentina Both McCarrison and Stanbury noted that, with an improved standard of living, more articles of diet were imported into the district and, containing iodine, lessened the incidence of goitre Thus, in the endemic areas of the world, the poorer the individual the bigger is his goitre

These great endemics can be imitated in miniature in the laboratory by giving rats a low-iodine diet, where the decreased output of thyroxine by the thyroid gland leads to increased activity of the basophil cells of the anterior lobe of the pituitary gland, with a proportionately increased rate of secretion of thyroid-stimulating hormone (T S H) This enhanced activity of the pituitary gland explains the postmortem observation made by Nièpce (1851) that cretins have large pituitary glands

In my own laboratory we have maintained rats for two years on a low-iodine diet, killing them at intervals and attempting to reproduce the stages in the development of nodular goitre seen in man (Taylor and Poulson 1956) Unfortunately we found that the thyroid gland of rats behaved like a single human thyroid lobule, and hyperplasia was uniform and not focal, we obtained nodules, but they were not hyperplastic However, it led to an investigation of the individual items in the diet we found that calcium carbonate, which is a usual constituent of rat diets, is very goitrogenic in young animals on a low iodine regime (Taylor 1954) This observation correlates well with the fact that in the low-iodine areas of the world, where there is much chalk or limestone, goitre is more common—e g , Derbyshire How salutary it is to read the work of Boussingault (1831), who mapped out the goitrous areas of Colombia and related them to the presence of limestone

Since the nodules in goitre appear to be related to increased secretion of T S H , we have been taking excised thyroid glands straight from operating-theatre to laboratory Tissue slices of nodular and non-nodular tissue have been studied in a Warburg apparatus, but no technique that we have evolved has shown a difference in the responsiveness of the two kinds of tissue to T S H (Taylor and Moffitt 1957) An interesting study by Pitt Rivers et al (1957), using chromatography on excised nodules, has disclosed a larger proportion of the precursors of thyroxine, suggesting that the metabolism of iodine in some of these active areas is abnormal

Treatment

The foregoing account makes it possible to be rational in the treatment of simple nodular goitre Prevention being better than cure, an adequate daily intake of iodine is the most important single factor and one which can be readily provided by iodising all domestic salt Puberty goitre and diffuse enlargement of the thyroid gland calls for either gr 3 of desiccated thyroid or sodium *l*-thyroxine 0 3 mg by mouth daily Claims have been made that triiodothyronine 90 0 µg daily is more effective, but in our hands its only merit has been swiftness of effect (When hæmorrhage has taken place into a nodule, the blood-serum should be aspirated through a wide-bore needle, usually nothing further is required) Finally there is thyroidectomy, which is usually indicated for cosmetic reasons, pressure effects, or suspected malignancy It is useless to enucleate single nodules, partial resection of both lobes and the isthmus is necessary When only one lobe is removed, often the patient returns in about five years with enlargement of the opposite lobe.

Since thyroid nodules appear to be due to compensatory hyperplasia, removal of thyroid tissue would deprive the patient even further of an already depleted supply of thyroxine It is true that nature compensates for this remarkably well, but a careful follow-up of patients after thyroidectomy for simple goitre usually shows a brisk increase in weight and fatiguability—a condition readily treated with small doses of thyroid, which may often be gradually reduced after a year or two The patient with a solitary hyperfunctioning nodule presents an extreme example of this, often becoming overtly hypothyroid after operation and, if uncorrected, taking at least three months to regain the euthyroid state The value of thyroid medication in the postoperative period has not been emphasised sufficiently in the past

The Toxic Nodule

Hyperthyroidism due to a solitary toxic nodule is rare, Plummer (1928), of the Mayo Clinic, first drew attention to it It is a condition comparable to that described in stage II, the "toxic nodule in a non-toxic gland", but in this case the mass of functioning tissue is so great that the patient is toxic. Hæmorrhage is usual in this type of nodule, and often the result is spontaneous cure of the hyperthyroidism Most clinicians must have seen the hyperthyroid patient who spontaneously lost all her symptoms I would go so far as to say that this is a self-limiting form of the disease

The toxic nodule is the only one which it is completely justifiable to enucleate, the remainder of the gland being left intact However, the remainder of the gland is atrophic, and its activity is suppressed by the secretion of the toxic nodule Therefore after operation the patient rapidly becomes hypothyroid and may feel acutely depressed Thyroid medication should be started in the immediate postoperative period and gradually diminished in the succeeding twelve months

The Malignant Nodule

The difficulty of deciding when a thyroid nodule is malignant has led to a spate of articles on this subject in recent years, indeed the incidence of malignancy in excised thyroid nodules has been reported at levels varying from 0 to 25% by different workers Crile (1950) was the first to point out that such figures merely reflect the habits of the surgeon, the cancer-rate depending directly on which patients he chooses for operation Certainly this greater alertness to the possibility of malignancy in the thyroid nodule must have encouraged many pathologists to take more blocks of tissue and to cut more sections

Ætiology

Since increased secretion of T.S.H can lead to focal hyperplasia in the thyroid gland, it seems possible that a continuation of the process might play an important part in producing malignancy If this is true, thyroid cancer should be commoner in areas of endemic goitre, and evidence has been marshalled in support of this by Doniach (1956) Switzerland, an endemic goitre area with a population a tenth of that of this country, has a death-rate from thyroid cancer almost identical with ours Furthermore the introduction of iodised salt in Switzerland is beginning to cause a decline in this incidence (Wynder 1952)

A malignant nodule in the thyroid gland has usually a papillary or follicular pattern Papillary carcinomas tend to occur in the younger patients, are non-encapsulated, grow relatively slowly, and spread typically by the lymphatics Follicular carcinomas have capsules which enable them to be shelled out from the gland, and their metastases are commonly blood-borne to bones and lungs Anaplastic carcinoma need not concern us here, because it does not usually present as a nodule

Diagnosis

The correct diagnosis of malignancy in a thyroid nodule is difficult, but the patient's complaint that all is not well in the neck should not be lightly dismissed Hardness, fixity, involvement of other structures, especially the recurrent nerve, all point to malignancy, as does involvement of lymph-nodes Radioiodine has some diagnostic value here because malignant tissue does not usually take it up in the presence of normal thyroid tissue, and thus a careful scan of the patient's neck with a collimated tube, as first described by Dobyns and Lennon (1948) (Taylor and Stewart 1951), may be helpful. If the nodule takes up radioiodine it is unlikely to be malignant Raymond Greene (1957) has reviewed his experience with this technique

Treatment

Whenever a nodule is suspected of harbouring papillary carcinoma, the whole lobe in which it lies should be excised, with careful preservation of the recurrent nerve If any lymph-nodes are involved they should be excised at the same time When follicular carcinoma is discovered it should never be shelled out, but total thyroidectomy should be done, with preservation of some parathyroid tissue The object of total thyroidectomy is twofold, it removes the primary tumour, and, if metastases are already present or develop later, they may be amenable to treatment with radioiodine if the thyroid gland is not there to compete for the isotope

The Prevention of Nodules

When the daily intake of iodine is less than about 100 µg, goitre becomes endemic, more especially where goitrogens, such as calcium, are present in the diet Goitre brings with it a host of complications increased incidence of thyroid cancer, probably increased incidence of hyperthyroidism, all the disability caused by pressure on the trachea, great vessels, and œsophagus, and cretinism (*Bulletin of the World Health Organisation* 1953) Because of these complications New Zealand, Switzerland, the United States, Yugoslavia, and Argentina now iodise their salt. The experience of those countries which have had iodised salt for years is the best proof of its advantages

There are no recorded adverse effects to man of adding 50–100 µg of iodine to the daily diet Although such effects have occasionally been claimed they have, on investigation, been shown to be due to some other factor, usually the addition of pharmacological instead of physiological amounts of iodide Unfortunately iodide added to table salt tends to migrate into the paper or cardboard container, but the use of iodate obviates this If any person wished to use salt without this addition, it could readily be arranged for such salt to be available on demand

The cost to this country annually of not iodising salt must be immense if calculated in terms of demands made on the medical services and loss of working time Why do we not iodise salt? The Medical Research Council recommended it in 1944 and again in 1948 An Order in Council was prepared in 1950 but never completed, the time has now come when we can no longer afford to postpone it

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POSTBULBAR DUODENAL ULCERATION

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THE diagnosis of postbulbar duodenal ulcer is often missed, and, as a result, patients with a severe and even lethal disability may be regarded as neurotic Even laparotomy may fail to demonstrate the ulcer, confirming the erroneous clinical impression Nevertheless, diagnosis is nearly always possible by radiography if appropriate techniques are used, especially if the clinician and radiologist are fully aware of the pitfalls in the diagnosis and work closely together to avoid them

Before discussing the radiological features, the limits of the duodenal bulb must be defined, so that a clear idea of what constitutes postbulbar territory can be obtained

The first part of the duodenum extends backwards for a short distance from the termination of the pyloric canal In this part of the course it usually runs horizontally, though it may have an upward or even slightly downward inclination Then, at the genu, the duodenum turns vertically downwards in its second part (fig 1)

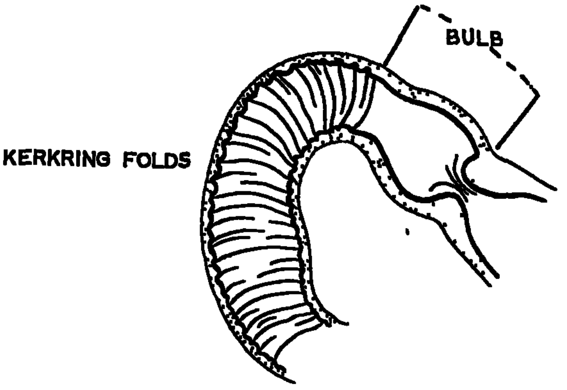

Fig 1—Diagram showing first and second parts of duodenum, with annular folds beginning at distal end of bulb

The bulb forms about two-thirds of the first part of the duodenum and is defined by the mucosal pattern The mucosal folds in the bulb run roughly parallel to its long axis, whereas beyond the bulb the folds become transverse and much coarser in texture The point of this transition marks the junction of bulb and postbulbar area We are here particularly concerned with ulcers in the immediate postbulbar area and genu, where they are most difficult to demonstrate radiologically Any backward inclination of the duodenal bulb tends to align the immediate postbulbar area with the bulb itself or even the pyloric antrum in hypersthenic patients Ulcers do arise in the second and third parts of the duodenum, but they are rarer, and easier to detect

Postbulbar ulceration cannot be excluded until the immediate postbulbar area has been fully displayed In practice, by using a small quantity of barium cream, and taking serial films of the postbulbar region in more or less exaggerated prone and supine positions, one can examine this area effectively without its being obscured by the bulb or pyloric antrum An overfilled stomach may make examination impossible A technique which we have found of value in extremely difficult cases, especially in hypersthenic patients, is to give a small quantity of barium cream, manipulate this into the bulb and second part of the duodenum, and then inflate the stomach through the stomach-tube After suitable rotation of the patient, the postbulbar area can be visualised through the air-inflated pyloric antrum If satisfactory results cannot be obtained in this way with the patient erect, the same technique can be used in the supine or prone positions (figs 2 and 3)

Fig 2—The ulcer is clearly seen through the air-inflated pyloric antrum (patient supine)

The two cardinal radiological features are the demonstration of the crater itself and of any localised stenosis of the duodenum near the ulcer In addition, it may be possible to appreciate local alteration of the mucosal-relief pattern around the ulcer The appearances of the crater are similar to those found in the bulb and require no further description The local stenosis, which is usually present, must be distinguished from incomplete filling of the duodenum or constriction due to normal peristaltic waves

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* Working on a grant from the Medical Research Council

Differential Diagnosis

A *diverticulum* is the most common source of confusion, but differentiation should be possible because of the smooth rounded outline, the absence of any local stenosis of the duodenum and the normal mucosal folds running into the diverticulum. A careful mucosal study is necessary to show this It may be possible to show the neck of the diverticulum. Finally the site is important, the diverticulum being commonest in the second part of the duodenum and rarest in the immediate postbulbar area

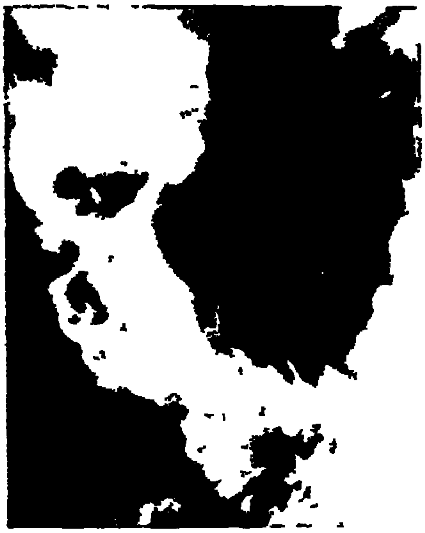

Fig 3.—A fairly large postbulbar ulcer seen through the air-inflated pyloric antrum (patient supine)

An *adhesion band* may constrict the duodenum to produce an area of stenosis, but absence of an ulcer crater and of mucosal changes should serve to avoid confusion

Carcinoma of the pancreas may produce a constriction of the duodenum Other features must be looked for, especially forward displacement of the duodenal loop and widening out of the arc of the duodenum.

Annular pancreas may cause confusion as it constricts the duodenum. Absence of a crater and dilatation above the constriction are the points to look for

Malignant tumours of the duodenum will show irregularity of contour of the growth and possibly irregular translucent areas due to protrusion of growth with the lumen. Also the stenosed area may be more diffuse than is the case with an ulcer

Benign tumours may produce rounded translucent areas with no evidence of stenosis

Case no	Sex	Age	Length of history (yr)	No of haemorrhages before diagnosis	No of barium-meal examinations	Night pain	Back pain	Intermittent obstruction	Gastric HCl
1	M	52	20		8	—	—	—	Low
2	M	65	5		1	—	—	—	N.K.
3	M	47	6	2	1	—	—	—	High
4	M	38	6	1	3	—	—	—	High
5	M	64	12	1	2	—	—	—	High
6	M	47	5	2	3	—	—	—	Normal
7	M	2[illegible]	4	1	2	—	—	—	High
8	M	62	18		5	—	—	—	N.K.
9	M	47	21		3	—	—	—	High
10	M	47	4	2	3	—	—	—	Low
11	M	22	8		3	—	—	—	N.K.
12	M	59	31	4	3	—	—	—	N.K.
13	M	75	20	3	4	—	—	—	High
14	M	4[illegible]	3	1	3	—	—	—	N.K.
15	M	68	4	1	3	—	—	—	High
16	F	45	13	1	3	—	N.K.	—	N.K.
17	M	69	40	2	1	—	—	—	N.K.
18	M	41	12	1	4	—	—	—	N.K.
19	M	54	10	1	4	—	—	—	N.K.
20	M	33	7		3	—	—	—	N.K.
21	F	35	6		3	—	—	—	High
22	M	75	35		2	—	—	—	Normal
23	M	47	3		2	N.K.	—	—	High
24	M	63	10	1	3	—	—	—	N.K.
25	M	29	3		1	—	N.K.	—	N.K.

N.K., not known.

At the Central Middlesex Hospital, in the year 1949–55, 25 cases of postbulbar duodenal ulceration were diagnosed

Features of Postbulbar Ulcers

Incidence

Increasing awareness of the lesion has improved our standards of diagnosis considerably 10 cases were diagnosed during the five-year period 1949–53, in 9732 barium-meal examinations, but 15 cases during the two years 1954–55, in 4016 examinations

Portis and Jaffe (1938) in a series of 9000 necropsies with 158 duodenal ulcers, found that 5% of the ulcers were beyond the bulb Perry and Shaw (1893), in their large series of necropsies, found 12% of duodenal ulcers beyond the bulb Brule et al (1936) collected 94 cases of ulcers in the second part of the duodenum, of which 84% were ampullary As Preiskel 1952) points out, there is a wide difference between the pathological and the radiological incidence

Age-incidence—Most workers agree on the high average age of patients with postbulbar ulcers Samuel 1952), with whose series ours is most comparable, gives 54 as the average age of his 12 patients with a range of 22 to 82 He attributes this high average age to delay in diagnosis, and we agree. The average age in our series is 51 2 (range 22 to 74) (see table)

Sex-incidence—Our 25 patients comprised 23 men and 2 women, a much higher ratio of men to women than is the case with duodenal ulcer in its more usual site.

Length of History

The average length of history in our series was just over twelve years, with a range of three months to forty years Samuel comments that in 5 of his 12 cases the history was longer than five years, and in 3 longer than twelve years Again we feel that this high figure is due to delay in diagnosis

Clinical Features

These patients' symptoms are generally severe and distressing The most common is pain

Night pain was present in 20 patients It was generally in the back or right scapular region, occasionally in the hypochondrium, often felt only at night. It was difficult to relieve, and more often only transiently relieved by alkalis or food, or occasionally by some unusual drink—e.g , case 1 obtained relief by taking "liver salts'

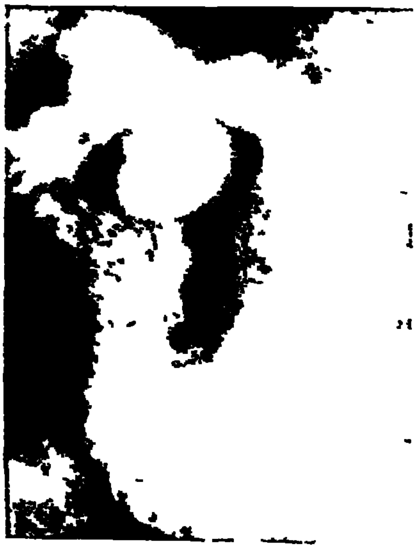

Fig 4—Case 6 the ulcer is just beyond the apex of the bulb There is also stenosis of the lumen of the duodenum in the region of the ulcer (patient prone)

Back pain was the second most common symptom, and was felt anywhere from the right loin to the left scapular region. It was severe and difficult to relieve by food and alkalis It might at first be periodic in character, with several weeks' freedom between attacks, but later became more frequent and might be felt daily

Hæmorrhage —15 of our patients at some time had hæmatemesis or melæna, generally the latter, and bleeding was severe and difficult to control In case 6 (fig 4) and case 13 (fig 5), emergency surgery had to be undertaken

Case 13 —A retired business-man, aged 75, attended the outpatient department in March, 1954, with a twenty-year history of severe attacks of pain and vomiting, especially when he was worried The pain was mostly in the back and kept him awake for a considerable time at night at first it was relieved by food and alkalis but later these were of little use In 1953 he had had a severe attack of melæna, for which he had a blood-transfusion Three barium-meal examinations were all negative, though a clinical diagnosis of duodenal ulcer had been made

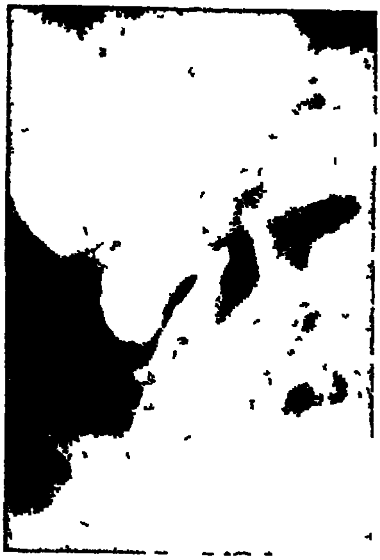

Fig 5—Case 13 the ulcer is in the immediate postbulbar area, with much local stenosis of the duodenum (patient supine)

In March, 1954, a barium-meal examination at the Central Middlesex Hospital showed a large ulcer crater in the second part of the duodenum on the medial side and a deformed duodenal bulb Much duodenal stenosis was evident In view of his age, obesity, and hypertension he was felt to be a poor operative risk and he was followed up as an outpatient He kept reasonably well until October, 1954, when he had a hæmatemesis and was admitted to hospital He settled down quickly and was anxious to return home without further treatment He remained well until December, 1954, when he was again admitted, this time with a severe hæmatemesis and melæna, which continued for some days Despite his poor general health it was felt that operation was essential to save his life The operation was technically very difficult A large ulcer was present in the second part of the duodenum which extended into the bulb The ulcer was nearly 3 in long, and this made closure of the stump very hard The stump broke down within a few days and the patient died some three weeks later

Intermittent duodenal obstruction —5 patients in this series had a history suggesting intermittent upper intestinal obstruction—severe sudden pain and continuous vomiting lasting up to four days, with gradual recovery They were generally quite well between the attacks In all, pyloric stenosis was diagnosed eventually, but 2 were submitted to laparotomy before a correct diagnosis was made These 5 form a subgroup which we feel could be diagnosed clinically All of these cases showed narrowing of the duodenum at the site of ulcer radiologically

Case 4 —A postman, aged 38, attended the Central Middlesex Hospital in 1951 with a slight hæmatemesis and melæna A barium-meal examination showed a large ulcer crater in the second part of the duodenum He remained well for some time, but later developed very severe attacks of vomiting and back pain, which lasted several days and from which he completely recovered with no symptoms in between He had these attacks about six or seven times a year He moved away from this area and attended several other hospitals where he had three negative barium-meal examinations and where neurosis was diagnosed twice and intestinal obstruction once At this time a laparotomy was performed but nothing abnormal was found and no further operation was undertaken

Soon after leaving the hospital he had a further attack and came back to the Central Middlesex Hospital, where a barium meal confirmed the presence of an ulcer and he was admitted for a partial gastrectomy At operation no ulcer was apparent from the external appearances, though the surgeon noted a slight thickening of the head of the pancreas Later an ulcer was felt in the posterior wall of the second part of the duodenum Again difficulty was experienced in closing the stump, and for a few days postoperatively there was a slight leak from the suture line Soon, however, he made full recovery and when seen later said that he "was a new man"

Duodenal obstruction may become persistent if allowed to continue for long without treatment

Case 8 —A retired business-man, aged 62, had an eighteen years' history of pain and intermittent attacks of vomiting, becoming more severe, and nearly continuous for the year before operation At operation a postbulbar duodenal ulcer was found and the second part of the duodenum was very narrowed and fibrosed

Perforation occurred in 1 case (case 6), coincidentally with a severe hæmatemesis The perforation was discovered at emergency operation

Associated Conditions

Diabetes mellitus —2 patients (cases 5 and 23) also have diabetes mellitus, in case 23 this developed at the same time as his symptoms of postbulbar ulcer Case 18 has a low renal threshold for glucose and may have diabetes We are not prepared to draw any conclusions from so small a number of cases

Peptic ulcer —Outside this series of 25 patients we have seen 4 others with a coincidental ulcer in the bulb These have not been included in the series because we felt that the clinical findings might be obscured by an ulcer in the more usual site

Investigations

Barium meal —The table shows that the average number of barium-meal examinations carried out in our patients before a diagnosis was made was 3 (range 1 to 8) Taken in conjunction with the rest of the clinical history, this itself is a suggestive feature

Gastric hydrochloric acid —Test meals were given to 13 of the patients, but did not prove a real aid to diagnosis 9 patients had a high acid curve, 4 had a low curve

Treatment

In postbulbar duodenal ulcers medical treatment is usually unsatisfactory, operation is indicated in most cases, and should be undertaken when the patient is relatively well

7 patients in this series have had gastrointestinal operations

1 had a gastroenterostomy because he was a poor operative risk He has subsequently done very well

6 patients had a Polya partial gastrectomy 2 of these were operated on as emergencies for severe hæmorrhage, 1 also had perforated his postbulbar ulcer Both were severely ill at the time of operation and both died later The remaining 4 have done very well, though 3 had a stormy postoperative period with leakage from the duodenal stump in 2 cases

These operations are often technically difficult The identification of the ulcer may not be easy, and becomes harder the further away from the bulb the ulcer is situated The actual closure of the duodenal stump also presents difficulties, for at operation the ulcer is often found to have extended into the bulb, making proximal closure impossible In such cases, Bancroft's operation may be helpful the pyloric antrum is divided about 1 in proximal to the pylorus, and the mucosa is cored out before closing the stump

Summary

25 cases (23 in men and 2 in women) of postbulbar duodenal ulcer have been studied

Postbulbar duodenal ulcers comprise all those that arise in the duodenum beyond the bulb, though this article is mainly concerned with those in the immediate postbulbar area

Diagnosis depends on awareness of the disease and cooperation between clinician and radiologist

Two groups can be separated out in which a tentative clinical diagnosis can be made

Hæmorrhage group Typically the patient is a middle-aged man with a long history of pain, one or more attacks of bleeding, and usually several negative barium-meal examinations

Intermittent obstructive group Typically the patient is a middle-aged man with a long history of attacks of profuse vomiting and severe pain lasting a few days He is relatively well between attacks, and has usually had several negative barium-meal examinations

The most important symptom is hæmorrhage, for it is often severe and hard to control by medical means Elective partial gastrectomy, if possible, is indicated in most cases

Perforation is rare

We are very grateful to Dr F Pygott and to Dr F Avery Jones for permission to publish these cases, and for their help in the preparation of this article We should also like to record our thanks to Mr J W P Gummer for his advice in the surgical aspects

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FLEXION SPASMS AND CONTRACTURES IN SPINAL-CORD DISEASE

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THE late stages of spinal-cord disease—e g, disseminated sclerosis—are often associated with extreme degrees of flexion and adduction deformity of the legs Contractures and spasms combine to cause pain, and they may make the sitting position impossible Distress and deformity are often made worse by loss of sphincter control and bedsores

We have attempted to deal with scores of such patients in recent years, and, since the methods used have slowly become much more effective, it seems desirable to record briefly some of our conclusions

Prevention

We are increasingly aware of the possibilities of prevention Thus a patient with spastic paraparesis who can stand and walk a few steps every day will maintain a predominance of tone in extensor muscles sufficient to prevent any serious tendency to develop flexion spasms Should, however, such a patient have to go to bed even for a few days—e g, on admission to hospital—the lack of standing exercise apparently allows the flexors to ' take over " If the dangers of this situation are not recognised, the spastic flexor muscles quickly shorten, contractures develop, and the patient may never again be able to stand or walk Thus, in cases of spinal-cord disease causing severe paraplegia, a day or two in bed may lead to the permanent loss of all capacity to be other than chair-ridden or even bedfast Hemiplegics, on the other hand, should not be allowed to develop flexion deformities, because all hemiplegics can walk a little, if their general condition allows, and this stimulus maintains extensor tone in the affected leg

When, however, going to bed is unavoidable in a patient with spinal-cord disease, several measures should be taken to counter flexion spasms In the first place, if the general condition permits, a few minutes' weight bearing every few hours is of great value Secondly, all such patients should lie prone for several separate periods each day according to the severity of their disease This posture provides a very powerful counter to flexion movement both by the physical factors involved in this posture and by a physiological tendency for this posture to inhibit flexion It is advantageous to arrange the bed so that the feet hang over the end of the mattress Where adduction spasm is troublesome, pillows may be used to force the knees apart.

The sitting position, in bed or in a chair, should only be allowed for limited periods, because this encourages shortening of these muscles Further, the sitting position increases the hazard of bedsores owing to the increased weight on the buttocks

Correction of Contractures

Once contractures have formed, it is necessary to introduce some extra mechanical force to counter the deforming effect of the muscles involved There are many different ways in which this can be done, but we feel that the following principles may be identified

(1) Prolonged gentle pressure by springs, traction, or turnbuckle plaster is not usually suitable, because the skin will not tolerate the forces required

(2) The skin will, however, tolerate great pressure for limited periods If skilfully applied, such pressure constitutes a very powerful means of countering and correcting flexion contractures Thus, a pressure of 100 lb applied by sling to knee or ankle is well tolerated for 30 minutes, three or four times daily, and this can with advantage be followed by a period of lying prone

(3) One very effective method of pulling out the contracture at the knee, which often develops, is to place the patient prone and to hang a weight on the heel, which is projecting beyond the end of the mattress This effect is increased if vertical upward pull is exerted on the knee through a sling-and-pulley system connected to a weight

(4) Heavy weights might, however, in certain circumstances tear through some of the contracted tissues, so the method described by Russell and Schuster (1951) is safer because the amount of pull is measured and, if the tissues give way, the strength of the traction immediately decreases

Thanks to the devoted work of both physiotherapists and nurses, these and other similar methods have had some striking successes, but for the worst cases several months' treatment has been necessary to pull out the contractures The following case illustrates this

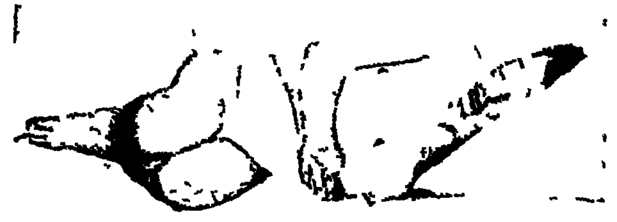

Fig 1—Case 1 condition on admission (April, 1956) showing degree of flexion contracture

Case 1—A soldier, aged 22, contracted tuberculous meningitis while serving in the Army abroad He was evacuated by air on Jan 25, 1955, to the Military Hospital, Wheatley, and admitted under the care of Dr Honor Smith He deteriorated considerably during the flight and was semi-comatose on arrival A prolonged and stormy illness followed Its course was complicated by spinal block of long duration, persistent vomiting, an episode of cerebral hæmorrhage causing dysphasia after intraventricular therapy, decorticate attacks probably of vascular origin, and renal infection with profound disturbance of electrolyte balance During the acute stage of the disease he had more than 350 lumbar, cisternal, and ventricular taps However, the infection was eventually eradicated, and he was admitted to Stoke Mandeville Hospital for rehabilitation on April 6, 1956, fifteen months after the onset of his illness

On admission his general condition was fair, but he was thin and content to lie in bed He had little dysphasia and was partly oriented in time and space but was amnesic for the whole of his time in hospital and abroad (about two years) He read J1 with each eye Both fundi showed mild optic atrophy He had slight bilateral deafness The movements of his arms were excellent In relation to the spinal block which developed during his illness there was now spastic paraplegia and his legs showed severe flexion contracture (fig 1) Strong manual force was needed to overcome the spastic element, but there still remained about 60° of fixed contracture at both hip and knee There was no sensory loss in the legs

Treatment—The deformity was lessened a little each day by various forms of therapy, including repeated stretching on the appliance designed by Russell and Schuster (1951), colloquially known as the "rack" by the ward staff The name is inaccurate because its action is not one of traction, but is exactly comparable to that of applying a downward pressure on the knees of an oarsman on a sliding seat It differs in that the patient lies on his side and the force is applied hydraulically and is virtually isometric

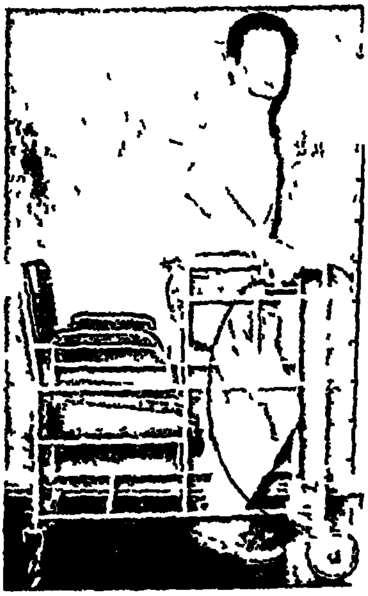

Fig 2—Case 1 in July, 1956

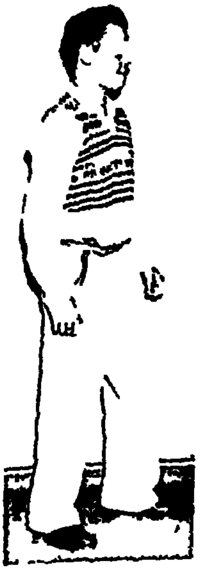

Fig 3—Case 1 in December, 1957

Progress was slow, but the contractures yielded slowly By July, 1956, the patient could move a little in walking plasters, and in December, 1957, he was walking well without plasters Spastic paraparesis persisted but with minimal contracture (figs 2 and 3)

Surgical Operations

Attempts to correct flexion contractures by operation have encountered difficulties Thus division of tendons is often disappointing, and rigid splinting to maintain improved posture after operation may cause necrosis of skin unless the procedure provides sustained reduction of the flexor spasms

It must also be appreciated that discomfort from the surgical incision stimulates flexion spasms vigorously, and the results in the past have often been disappointing

Division of the obturator nerves, however, gives striking relief to the patient who develops severe adduction spasms

Division of lumbar and sacral motor roots relieves all spasm in the legs, without loss of sensation, but the gluteal muscles waste so severely that sitting becomes uncomfortable Large intrathecal injections of alcohol to destroy cauda equina are used in cases of complete transection of the cord (Guttman 1949) but are not suitable for the partial lesions considered here

A striking success has been achieved recently by a combination of operations including neurectomy, tenotomy, and tendon transplant The groups of muscles *most amenable to surgical treatment are the adductors* and flexors of the hip, the hamstrings, and the calf muscles, and the operations used include the following

(1) *Adduction and flexion of the hip*—Obturator neurectomy (Stoffel 1912) alone will relieve adductor spasms, and in bilateral cases without contracture the abdominal approach is used In our cases, however, there is usually contracture of both the adductors and the hip flexors, and for this to be relieved it is necessary to divide the tendon of the iliopsoas muscle to relieve shortening or spasm of this muscle An incision is made over the tendon of the adductor longus muscle, the origins of the adductor longus and brevis muscles are separated from their bony attachments, the anterior and posterior divisions of the obturator nerve are then divided By following the upper border of the adductor magnus muscle one is led to the insertion of the iliopsoas muscle, which can then be divided In closing the wound the origins of the adductors are not sutured back into place After operation gentle assisted abduction and extension, combined with lying prone are practised on the day following operation Standing out of bed is begun on the third day

(2) *Flexion of the knee*—The insertions of the biceps, semitendinosus, semimembranosus, and gracilis muscles are transplanted to the femoral condyles by the technique of Eggers (1952) This may be combined with section of the branches of the posterior tibial nerve to the gastrocnemius muscle After this operation a plaster is well tolerated and is applied from the groin to the toes This is removed after two weeks, and active extension of the knee is begun together with lying prone

(3) *Spastic equinus*—This condition can often be relieved by simple tenotomy of the tendo Achillis This operation causes a shuffling gait with loss of spring in the foot, but this is of little importance in chair-ridden patients This operation may not only relieve painful spasms but also may enable the patient again to walk a little with assistance

Illustrative Cases

The following case-reports illustrate the outstanding advantages of selecting a combination of these operations for cases which do not respond to simple non-surgical methods

Case 2.—A man, in whom multiple sclerosis presented with difficulty in walking in 1937 at the age of 24, walked sufficiently well to be accepted into the Army in 1939 but was invalided in 1941 because his legs became weaker From that time onwards he became steadily worse and he last walked in 1952 with assistance In this year there was an episode of weakness in the left arm, which did not recover completely and so added to his disability He remained at work as a clerk, using an electric chair outside and a wheel chair indoors By 1957 flexor spasms of the legs had become so severe that it was difficult for him to sit in a chair The movement and pain caused by these disturbed his sleep and greatly impaired his efficiency at work

On admission to Stoke Mandeville Hospital on Aug 6, 1957, for assessment he obviously had severe discomfort and pain during the spasms He was demoralised by lack of sleep and appeared tired, pale, and older than his years The positive signs present were nystagmus on lateral and vertical gaze, severe spastic weakness of the left arm with sensory loss of posterior column type, spastic chest and abdominal muscles, and spastic paraplegia with a tendency to flexion contractures Flexor withdrawal of both legs was induced by even light touch on the foot There was little adduction spasm By firm manual restraint the knees and hips could be extended to a minimum of 15 of fixed flexion

Operation on the left leg was done by one of us (G P) on Aug 16, 1957, under general anæsthesia with relaxants The tendons of the biceps and semimembranosus muscles were implanted into the posterior aspect of the femoral condyles, and the nerves to the calf muscles were divided The tendon of the semitendinosus muscle retracted so vigorously into the wound that it could not be implanted A plaster-of-paris cylinder was applied to the limb from the groin to the toes

Postoperatively, incisional pain caused a temporary increase in spasms, but these were reduced by administering pethidine, and they became much less distressing after four or five days The plaster was removed a fortnight after the operation The incision and the skin were in excellent condition There was a striking relief of pain by three weeks after the operation The pattern of the spasm had altered completely, and the frequency was much less There was no flexion of the knee during a spasm The quadriceps was observed to contract, but this was not painful The spasm at the hip was less and no longer uncomfortable. There was little change in the right leg, but the patient could sleep prone for much of the night, which had been impossible before the operation On discharge on Sept 16, 1957, he was just beginning to stand again with assistance He was deliberately discharged to avoid too long an interruption in his employment

Follow-up—When he was seen on Oct 2, 1957, he was distressed by spasm in the other (right) leg and pleaded to have a similar operation on this side also This was done on Nov 8, 1957, the procedure being identical except that it was possible on this occasion to implant the tendon of the semitendinosus muscle in addition to the others

Postoperatively, pain made the spasms worse for a time, but the end-result was the same as that achieved on the left side The patient s general condition improved, and he began to sleep well again Both legs are still subject to slight flexion spasms at the hips, but the movement is small in amplitude He can sit comfortably in a chair and can lie prone quite easily He stood again with support four weeks after the second operation In March, 1958, the improvement was well maintained and he was again at work

Case 3—Multiple sclerosis presented in a woman aged 29 in 1939 with paræsthesiæ in the right arm and leg, stiffness aching, and weakness of the right leg, and weakness of the right hand From 1939 until 1954 or so she had a remarkable series of fluctuations and relapses, often with considerable remission in the intervals From 1954 her disability increased steadily because of increasing paraparesis with frequent flexion spasms causing severe pain in her legs and lower back. In 1954 she would walk several miles and do all her shopping In the three months before admission her walking became much worse.

On admission to Stoke Mandeville Hospital on Aug 25, 1957, at the age of 47, she could walk a few steps with assistance She complained of stiffness and pain in all the muscles from her waist downwards She had difficulty in winding a watch, and her writing had deteriorated considerably

On examination she was mildly euphoric and loquacious The right fundus was pathologically pale. She read J1 with each eye She had a slightly enlarged left pupil and slight left ptosis, but her external ocular movements were full Slight left facial weakness, minimal ataxia on the finger-nose test, and slight impairment of fine finger movement were noted The deep reflexes in her arms were increased except for diminution of the right supinator jerk. Sensation was impaired and was mainly moderate loss of posterior column function Her abdominal reflexes were absent, and her lumbar and abdominal muscles were slightly spastic A partial sensory level was found at T8, with mild loss of perception of all modalities below this Her legs showed severe spastic paraparesis with painful and distressing spasms of forced extension and adduction When these came on she had considerable low back pain. Her deep reflexes were increased, and she had ankle clonus and extensor plantar responses Her general condition was fair except for mild anæmia (Hb 76% = 11 2 g per 100 ml), but she looked tired and unwell

Progress—She unfortunately acquired influenza during treatment soon after admission, and this kept her in bed for a few days, during which she lost ground rapidly and flexion and adductor spasms became dominant over her weak powers of extension Progress with physiotherapy was so slow and she had such considerable distress and pain with the spasms that it was decided to operate

Operation—On Nov 8, 1957, under general anæsthesia the deformities of the hips and knees spontaneously corrected and there was little or no evidence of contracture An incision was made over the tendon of the adductor longus muscle on each side The tendon was divided from its origin and turned down to expose the anterior branch of the obturator nerve. One inch of the nerve was resected and the origin of the adductor brevis muscle was then divided and the muscle turned down to expose the posterior division of the nerve, which also was divided By following the upper margin of the adductor magnus muscle the insertion of the iliopsoas muscle was identified, it was found to be contracted and was divided The patient was then turned on her face An S-shaped incision was made over the popliteal fossa and upper calf on each side This type of incision is used to avoid subsequent contracture of the scar The insertions of the semitendinosus, semi-membranosus, gracilis, and biceps femoris muscles were identified and divided The first three tendons mentioned were transplanted into the posterior aspect of the medial femoral condyle, and the last-named tendon into the lateral femoral condyle The motor branches arising from the posterior tibial nerve, and supplying the [illegible] muscle were [illegible] and divided The [illegible]

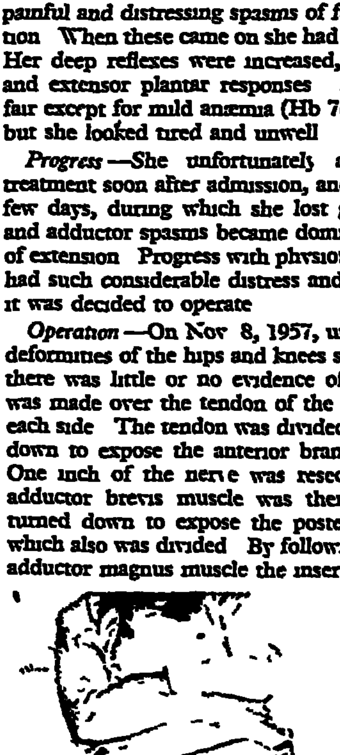

Fig 4—Case 3 preoperative posture during active spasms of right leg note considerable adduction of both legs

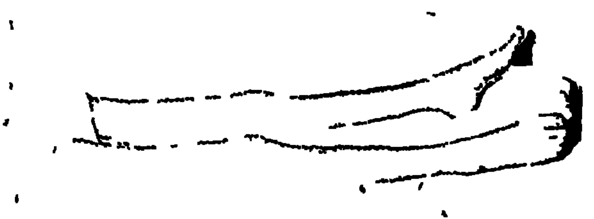

Fig 5—Case 3 postoperative absence of adduction, note extension of both legs (flexor spasm could not be induced)

were then closed, but no attempt was made to re-attach the adductor origins The knees were immobilised in the straight position by padded plaster cylinders

Postoperatively the patient's blood-pressure fell somewhat, and she required methylamphetamine, dextran, and blood to restore her circulation to normal This was probably the result of doing the operations on both sides at one session The patient had been turned twice during the operation There was incisional pain of some severity which caused increased spasm for about ten days, and she required pethidine frequently to control this However, after the plasters were removed, the incisions were found to be in excellent condition, and she began to improve As in case 2 perhaps the most striking improvement was in her general appearance This improvement was parallel with the lessening of her pain Flexion spasm was replaced by extension spasm which was not distressing She began to stand with plasters about three weeks after the operation and can now, five months after operation manage a few steps with assistance (figs 4–6)

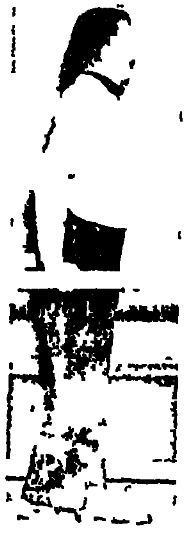

Fig 6—Case 3 standing supported after operation

Discussion

In case 1 the spinal-cord disease was completely arrested, and it proved possible to pull out severe contractures over a period of many months In retrospect, however, it seems that this good result would probably have been obtained more quickly with the assistance of surgery

In cases 2 and 3 there is progressive disease of the nervous system with no prospect of a good recovery of crural functions, and for these we used a combined operation to deal with all the main muscle groups affected This operation not only divided or paralysed the muscles causing deformity but also converted the hamstring muscles from knee flexors to thigh extensors The early postoperative results are most gratifying and much better than any we have achieved by other means Relief of both pain and spasm is most noticeable, and there is every indication that this type of operation can keep these unfortunate patients much more comfortable and active than would otherwise be possible

Summary

In non-progressive cases of flexion spasms good results may be obtained by mechanical devices which apply powerful correcting forces two or three times daily for periods of about 30 minutes each

In severe cases operation may give excellent results by one or all of the following procedures obturator neurectomy, division of the tendon of the iliopsoas muscle, transplantation of the hamstring tendons to the back of the femur, division of the nerves to the gastrocnemius muscle, and section of the tendo Achillis

These combined operations can be used to give great relief to patients with flexion contractures and spasms due to spinal-cord disease

We wish to pay a special tribute to the nurses and physiotherapists, whose tireless interest in helping the patients make these results possible

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INFLUENCE OF FASTING ON THE IMMUNOLOGICAL REACTIONS AND COURSE OF ACUTE GLOMERULONEPHRITIS

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Volhard (1937) claimed that fasting is one of the most effective means of treating acute glomerulonephritis, and this has often been confirmed After fasting, all the acute manifestations (reduction of glomerular filtration-rate (G F R), hypertension, and œdema) rapidly subside (Brod 1949), but we do not know why Volhard himself thought that an overtaxed circulation was unburdened, but this view is hard to sustain Because the rational basis of this treatment was uncertain, many physicians abandoned or changed it, and some have even suggested that acute fasting might hasten the development of uræmia, as happened in rats that were starved after partial nephrectomy (Persike 1950) or in experimental Masugi nephritis (Dutz et al 1956)

But in acute glomerulonephritis it is less important to prevent uræmia than to shorten the disease The ultimate prognosis of the disease depends on both the intensity and the duration of the acute stage (Brod 1949, Brod et al 1955) which, according to present opinion, is caused by an autoallergic vascular reaction We cannot influence the intensity, but every means of shortening the acute stage must be used

Since fasting seemed to have so great an effect, we thought it worth while to investigate whether fasting interfered with the capacity to produce an autoallergic reaction Many victims of the concentration camps, who had previously had allergies, lost them during their period on a semi-starvation diet (Šmahel 1946)

The autoallergic reaction in acute glomerulonephritis is accompanied by a raised serum titre of certain agglutinins (collodion agglutinins), which may represent anti-kidney antibodies (Cavelti and Cavelti 1945a and b, Lange et al 1949, Lippmann et al 1950, Wagner and Holečková 1951, Rejholec et al 1952) We have, therefore, followed the change of the titre of these agglutinins in the course of therapeutic fasting in acute glomerulonephritis, and compared the course of these changes with the course of the main clinical and functional manifestations of glomerulonephritis

Methods

The patients investigated were treated in our institute, or in the pædiatric department, with enforced strict bed rest Fasting was usually started 24 hours after admission During the first 24 hours in hospital, the patient was kept on a light diet, and basal data of his renal functions and (in most cases) collodion agglutinins were obtained The period of fasting lasted 60 hours, the patients received neither food nor fluid, except for some 100 ml a day of unsweetened fruit-juice They were given no glucose (Pevznĕr (1949) holds that glucose increases the likelihood of allergic reactions)

When the 60-hour period was over, the patients were put on a semi-starvation diet, consisting mainly of fruit and vegetables, and yielding no more than 500 calories, which was continued until all signs of the acute vascular reaction (reduced G F R, hypertension, and œdema) had subsided Only then did we go over to a normal diet or to the quantitative diet of Addis (1948)

As a control we used a group of children from the pædiatric department They were also kept strictly in bed, but were given a light diet with no fasting period Such a diet is used in the treatment of glomerulonephritis by most pædiatricians (Rabinovich and Winter 1950, Mores and Navratil 1952)

From the first day the G F R was estimated by the clearance of endogenous creatinine in 4-hour periods throughout the whole period of observation Daily Addis counts of the urinary deposit were made Blood-pressure and fluid-balance were measured daily

The titre of the collodion agglutinins was estimated (Cannon and Marshall 1940, Cavelti 1941, 1948, Humphrey 1948, Lange et al 1949, Wagner et al 1952, Wagner 1954)

Collodion stock suspension was prepared by the method of Wagner and Rejholec (1952) and Wagner (1954), it lasts 3 weeks This stock solution was diluted with 1 1% saline or Ringer's solution to McFarland's grade-2 density The antigen was prepared from a healthy human kidney, as free from blood as possible, ground up and diluted 1 4 with either saline or Ringer's solution This suspension was kept at −30°C On the day of investigation 1 part of this solution was added to 20 parts of the collodion suspension The antigen-collodion suspension was incubated for 1–2 hours at room temperature The serum to be investigated was diluted geometrically with the saline or Ringer solution To the diluted serum, an equal amount of the incubated collodion-antigen suspension was added (usually 0 25 ml are used) After 2 hours' incubation at room temperature, the test-tubes were centrifuged for 3 minutes at 1200 revolutions per minute The deposit was stirred and examined in reflected light without magnification If the particles were just visible, the result was ±, if the particles formed lumps of 1 5 mm in diameter, the result was ++++ The highest geometrical dilution of serum containing antibodies was usually ±, and this dilution grade is indicated in tables I and II But when there was agglutination at dilutions 1/16 and higher, the lowest dilution usually gave a ++++ result, with at least + in the 1/8 dilution The "dubious" 1/4 titre was the only one where only a ± result was sometimes obtained

Control specimens of the diluted collodion and the collodion-antigen suspension were always examined for spontaneous agglutination Normal sera always gave negative results A titre of 1 4, though never found in normal subjects, was regarded as a dubious result, a titre of 1 8 was regarded as positive (Lange et al 1949, Rejholec et al 1952) The highest titre observed by us in human glomerulonephritis was 1 128

Results

Patients Treated by Absolute Fasting

Of twenty-nine patients with acute glomerulonephritis, four were adults (aged 22–59) and twenty-five children (aged 5–15 years) In twenty patients, a positive titre of collodion agglutinins was found in the serum on the day of admission In two others, in whom the titre was first estimated on the 1st day of treatment, a positive titre was also found Another four had dubiously positive titres of 1 4 The initial titres were negative in only three

Of the twenty-six positive and dubious titres at the beginning of treatment, nineteen became negative immediately after the end of the fasting-period (table I) In

TABLE I—PATIENTS TREATED BY ABSOLUTE FASTING

Case No	Age (yr)	Sex	Days from onset of glomerulonephritis to fasting	Titre of collodion agglutinins		Days from fasting to disappearance of agglutinins	Days from start of disease to disappearance of agglutinins	Glomerular filtration-rate (ml per min)		Days from fasting till G F R became normal	Blood-pressure (mm Hg)		Days from fasting till B P became normal	Œdema		Days from fasting till œdema disappeared	Remarks
				Before fasting	After fasting			Before fasting	After fasting		Before fasting	After fasting		Before fasting	After fasting		
1	7	F	3–4	1 8	0	4	7–8	10 7	35 1	4	125/70	110/75		+	0	5	
2	10	F	7	1 8	0	1	8	43 7	46 6	14	180/130	115/80	2–4	+	0	2	
3	11	F	5	1 16	0	3	8	35 0	63 6	4	150/110	115/70	2–3	+	0	4	
4	11	M	5	1 64	1 16–0	6	11	45 8	75 6	2	160/130	135/60	7–8	++	0	6	
5	15	M	6	1 16	0	4	10	50 5	58 4	6	130/90	120/90	2	0	0		
6	8	F	8	1 8	0	5	13	14 9	42 7	3	140/100	115/85	2	++	0	3	
7	13	M	7–10	1 4	0	0–3	7–10	57 2	63 5	5	120/90	105/70		0	±		
8	8	F	2	1 32*	1 8–0	3	5		30 2	6	120/95	115/85		++	0	1	
9	11	F	4	1 4	0	0	4	42 9	56 8	6	150/100	120/70	2	+	0	2	
10	9	F	7	1 32	1 8	10	17		32 1	9	150/100	115/70	3	0	0		When fasting was stopped, the titre rose again
11	13	F	10	0	0	Neg	Neg	14 7	11 4		155/100	125/80	3	++	0	2	
12	48	F	1	1 128*	1 8	6	6	35 4	55 1	6	185/135	155/100		+++	+	6	History of hypertension before the onset of glomerulonephritis
13	8	M	13	1 4	0	1	14	18 8	28 0	5	115/60	95/60		+	0	1	
14	59	F	9	0	1 128	3		67 8	73 8	6	240/120	215/115		++	+	5	History of hypertension before the onset of glomerulonephritis
15	6	F	3–4	0	0	Neg	Neg	33 8	34 3	10	100/60	85/60		0	0		
16	41	M	5	1 8	0	3	8	99 3	110 0	5	170/100	165/95		+	0	4	
17	11	F	5	1 16	0	3	8	39 3	64 3	4	130/90	120/80	2	+	0	3	
18	7	M	8	1 4	0	1	9	30 5	27 2	12	120/75	120/75		+	0	2	
19	13	F	6	1 16	0	2	8	53 0	52 4		135/95	120/70		±	0		
20	7	F	15	1 128	1 128–1 4	7	22	25 7	42 9	7	170/120	135/80	7–8	++	±	7	When fasting was stopped, the titre rose again
21	8	M	5	1 64	1 4–0	6	11	56 3	47 9		150/120	120/90	3	+	±	10	
22	8	M	6	1 8	0	3	9	14 8	31 8	6	130/95	105/65	3	0	0	2	
23	9	F	4	1 8	0	1	5	37 4	45 3	8	130/70	115/70		0	0		
24	12	F	3	1 8	0	1	4	45 9	64 0	4	140/85	115/75	2	±	0		
25	22	F	4	1 16	0	4	8	97 3	80 0		130/95	115/90		±	0		
26	8	F	45	1 8	0	2	47	9 3	13 4	6	160/115	160/105	5	±	0		
27	6	M	61	1 16	0	2	63	11 3	35 9	4	135/95	125/90		++	+	10	
28	13	F	152	1 32	0	3	155	7 3	17 9	6	125/80	130/95		−	−		
29	8	M	31	1 16	±1 4	13	44		30 7	10	120/75	125/70		++ −	± −	5	

* First estimation on the first day of treatment Neg, negative

seven others the titres definitely decreased The average duration from the start of treatment to the time when the titres became zero was 5 days (range 1–13 days)

Of the twenty-six patients with decreasing titres of antibodies, reliable data on glomerular filtration were obtained in twenty-three By the first day after the end of the fast, the G F R definitely rose in sixteen patients, and in two more an upward trend was probable At the same time the blood-pressure fell to normal and the œdema subsided in all patients but one

A boy, aged 15, had had glomerulonephritis for 10 days when he was admitted Fasting was started 24 hours after admission (fig 1) The titre of the collodion agglutinins started to drop almost at once The G F R averaged 50 ml per min on the day of admission, after a transient fall on the first day of fasting, when the titre of antibodies was still 1 16, it began to increase on the second day and reached 91 ml per min 2 weeks later The blood-pressure, which was 130/90 at the start, fell to 110/70 He had no œdema There was no consistent change in proteinuria or in the Addis count

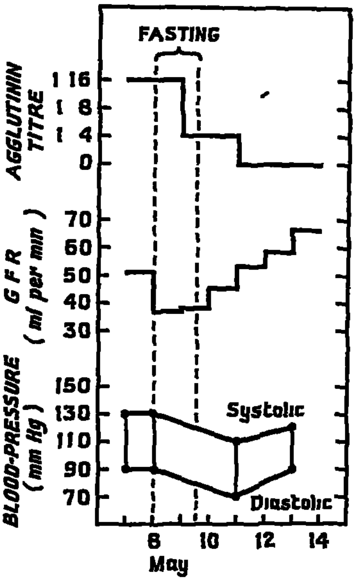

Fig 1—Course of illness in a boy who fasted

In three patients the antibody titre started to rise again when the fasting gave place to a light diet containing plenty of carbohydrate (fig 2)

In three patients whose antibody titres were negative at the start, the fasting had no effect on their G F R

Patients Treated with Bed Rest and Light Diet

This group consisted of nine children aged 5–14 On admission, the agglutinin titre was positive in five, doubtful in one, and negative in four (table II) But in all nine patients the titres became strongly positive in the subsequent days when the children, although resting, were fed a diet rich in carbohydrate

A girl, aged 9 years, had had acute glomerulonephritis for 4 days (fig 3) On admission her G F R was 42 5 ml per min, and the agglutinin test was negative But on the 3rd day of hospital treatment, consisting of bed rest and light diet, the titre became positive (1 8), and 3 days later it reached a maximum of 1 32 The agglutinins did not disappear till the 10th day, and it was from this day on that the G F R started to increase, though a few days later it fell to about 38 ml per min The fall in blood-pressure and disappearance of œdema were slow, lasting up to the 8th and 10th day respectively of the hospital treatment

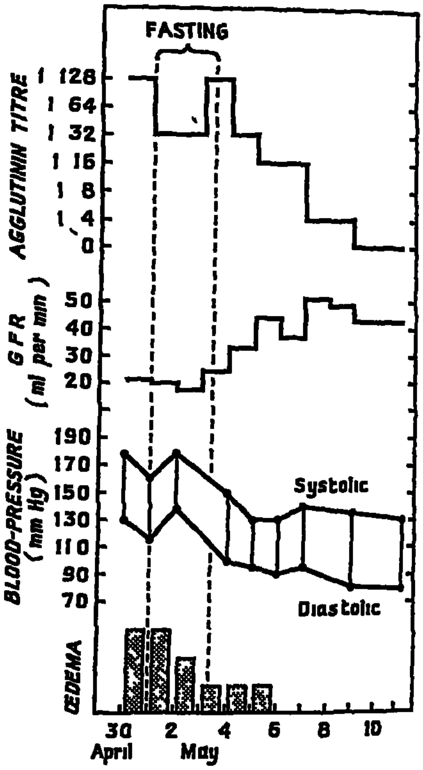

Fig 2—Rising titres when fasting was abandoned

A similarly slow disappearance of the signs of acute glomerulonephritis was found in eight of the nine patients In the 9th patient, a girl aged 13, no improvement was noted over 7 days Fasting was then ordered, and she improved quickly, but the disease became chronic

In three patients the glomerular filtration-rate was lowest at the start, in five there was a further drop during treatment, in one the course was interrupted by fasting, and in one (no 9) the changes could not be followed every day because of technical difficulties Of the eight patients in whom the G F R was followed long enough, there was an improvement in four 3–28 days after admission, but in none was the rate quite normal then Four patients had œdema, and it took 2–12 days to disappear The blood-pressure was raised at the start in five patients In three it subsided after 3–14 days, in one it remained permanently elevated, and in one hypertension disappeared when treatment was changed over to fasting

TABLE II—PATIENTS TREATED WITH BED REST AND LIGHT DIET

Case no	Age (yr)	Sex	Days from onset of disease to treatment (light diet and bed rest)	Titre of collodion agglutinins: Before treatment	Titre of collodion agglutinins: Maximal titre	Titre of collodion agglutinins: Days from admission to disappearance of agglutinins	Titre of collodion agglutinins: Days from start of the disease to disappearance of agglutinins	Glomerular filtration-rate (ml per min): Before treatment	Glomerular filtration-rate (ml per min): Lowest G F R	Glomerular filtration-rate (ml per min): Days from treatment to increase of G F R (new rate)	Blood pressure (mm Hg): Before treatment	Blood pressure (mm Hg): Days from treatment till B P became normal	Œdema: Before treatment	Œdema: Days from treatment till œdema disappeared
1	10	F	43	1 8	1 16	7	50	25 95	25 95	3 (35 9)	130/90	3	0	–
2	14	F	2	1 128	1 128	11	13	77 4	33 1	Not improved	175/125	Not improved	+ +	12
3	12	F	2	1 4	1 8	6	8	46 3	46 3	6 (73)	125/80	Normal	0	–
4	9	F	4	Negative	1 32	7	11	42 5	36 0	Not improved	140/100	14	+	8
5	10	M	21	1 8	1 16	26	47	55 4	42 4	28 (72)	125/85	Normal	±	7
6	5	F	1	Negative	1 32	9	10	23 8	19 8	10 (33)	90/50	Normal	0	–
7	10	M	8	1 16	1 32	10	18	28 5	28 5	Not improved	130/90	8	+	2
8	8	M	10	1 8	1 64	4	14	45 4	38 05	Not improved	110/65	Normal	0	–
9	13	F	7	Negative	1 16	–	–	55 8	Fasting		180/120	(Fasting begun)	0	–

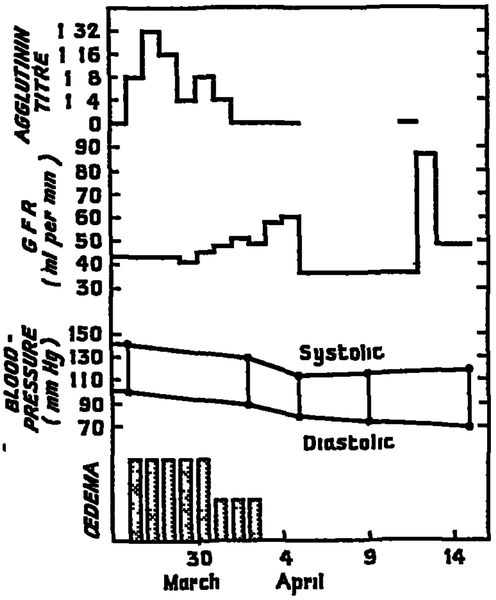

Fig. 3—Course of illness in a girl who did not fast

Discussion

The exact significance of the collodion agglutinins is uncertain, but there seems little doubt that they indicate the presence, and possibly the intensity, of autoallergic processes which form the basis of acute glomerulonephritis Fasting can clearly make these agglutinins disappear At the same time the main clinical manifestations of acute glomerulonephritis—reduced G F R, hypertension, and œdema definitely improved

On the other hand, in nine patients treated only by bed rest and light carbohydrate diet, the titre of agglutinins either remained unaffected or increased, and the clinical course changed more gradually The G F R rarely increased much or became normal within the period of observation Œdema and hypertension continued for longer

The differences between the two groups of patients were compared by the H-test (Wald and Wolfowitz 1944, Kruskal and Wallis 1952, Kruskal 1952), a means of variance analysis In the patients who fasted, collodion agglutinins disappeared significantly faster, and the G F R and blood-pressure returned to normal significantly sooner than in the control patients (table III) Œdema lasted, on the average, 4 2 days in the patients who fasted, and 7 3 days in those who did not, these differences are not significant

TABLE III—SIGNIFICANCE OF DIFFERENCES BETWEEN THE TWO GROUPS

—		Days after admission (average)		
		Disappearance of collodion agglutinins	Duration of	
			Reduced G F R	Hypertension
Fasting		5	6 3	3 6
Bed rest + light diet		10	11 7	8 3
Significance	H	8 271	7 081	5 348
	P	<0 01	<0 01	<0 05

Our observations suggest that therapeutic fasting may interfere with the autoallergic processes and thus shorten the duration of acute glomerulonephritis Further support for this view may lie in the fact that fasting had no effect whatsoever on the clinical course of three patients who had a negative titre of collodion agglutinins on admission (A similar negative result was found in two other patients—in the "latent" phase of chronic glomerulonephritis, with negative titres of antibodies—who were not included in the present series)

Brod (1949) has shown that, while direct manifestations of the generalised acute vascular reaction tend to subside, they leave residual damage in the glomeruli and tubular cells, this improves much more slowly or may become permanent Our data suggest that fasting has an effect only on the course of the early manifestations (reduced G F R, œdema, and hypertension), and does not reduce damage to the renal parenchyma caused in the individual patient by the initial vascular reaction But it seems established that one of the main factors in the ultimate prognosis is the duration of the initial acute vascular reaction in the kidneys We believe that our data show that fasting can shorten this acute stage, and that all patients with acute glomerulonephritis should fast

Summary

We describe a technique for estimating a titre of agglutinins which, we believe, indicate an autoallergic process underlying acute glomerulonephritis

Two groups of patients with acute glomerulonephritis were compared One group was treated by bed rest and light diet, the other was given no food for 60 hours In the fasting group, the agglutinin titre, blood-pressure, and glomerular filtration-rate all returned to normal significantly sooner than in the controls In three patients with normal initial agglutinin titres, fasting did not shorten the illness

We believe that fasting reduces the severity of the antigen-antibody reaction responsible for acute glomerulonephritis, and should be an essential part of treatment

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"Reflecting today on the case of a poor woman who had continual pain in her stomach, I could not but remark the inexcusable negligence of most physicians in cases of this nature They prescribe drug upon drug, without knowing a jot of the matter concerning the root of the disorder And without knowing this they cannot cure the patient Whence came this woman's pain (which she would never have told had she never been questioned about it)? From fretting for the death of her son And what availed medicines while that fretting continued? Why, then, do not all physicians consider how far bodily disorders are caused or influenced by the mind?"
—*The Journal of the Rev John Wesley* for May 12, 1759 London, 1909–16

CHANGES IN THE GALLBLADDER AFTER ELECTIVE GASTRIC SURGERY *

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After partial gastrectomy, ingestion of a mixture of hot milk and an egg—the fatty meal of the cholecystogram test—can produce a severe attack of " dumping " (Cox and Kerr 1957) The possible effects of gastrectomy on other digestive functions require study, and we have accordingly investigated the behaviour of the gallbladder, especially after a fatty meal, before and after elective gastric surgery

Investigation

Using intravenous cholecystography, two series of films were taken (in some cases three) in 18 unselected patients undergoing gastric operations The first series of films (the immediate preoperative) was taken within twelve days before operation, the second (the immediate postoperative) within twelve days after operation, and the third (the late postoperative) after an interval of not less than six months A series of films consisted of a two-hour fasting film showing the size and position of the gallbladder, followed by six films showing the rate of emptying after a glass of hot milk with an egg The reason for carrying out two series in some patients, instead of three, was the potential danger of excessive radiation, most patients having had a recent previous barium meal

Radiographic Technique

Light diet for three days, avoiding metallic medicines and gassy foods Early morning cup of milkless tea, then fasting for two hours before intravenous injection of ' Biligrafin ' (sodium salt of N N^1-adipic-di-(3-amino-2 4 6-triiodo benzoic acid)), 20 ml of 30% solution No food or drink for two more hours, then first film taken with patient prone Patient then given hot milk and whisked egg, and films taken at intervals of five, ten, fifteen, thirty, forty-five, and sixty minutes in identical position Radiographic factors 65–70 kV, 1 second at 200 mA , with cone

Results

Gallbladder Volume as Shown by Two-hour Film

Partial gastrectomy (*Billroth II, antecolic anastomosis with spur*) —9 cases In 7 there was an immediate preoperative and an immediate postoperative film In 6 of these, the immediate postoperative film showed dilatation of the gallbladder In the remaining case, there was no dilatation in the immediate postoperative film In 6 cases there was an immediate postoperative and late postoperative film The average time between the immediate and late postoperative films was fourteen months In 3 of these there was no increase in the size of the gallbladder, but in the remaining 3 the late postoperative film, compared with the first, showed dilatation of the gallbladder, indicating that the volume had increased since the operation

Partial gastrectomy (*Schoemaker*) —2 cases There was an immediate and a late postoperative film in each case The late film was taken ten months after the immediate In 1 case, the late film showed that the gallbladder had more than doubled its volume since the immediate was taken In the other, the late postoperative film showed no change

Partial gastrectomy and vagotomy —The anastomosis was antecolic with spur 4 cases, with a preoperative and a late postoperative film in each The average interval after operation before the postoperative film was thirteen months This late postoperative film in each case, compared with the preoperative film, showed that the gallbladder had doubled its volume

Vagotomy and posterior gastroenterostomy —3 cases, each with a preoperative and two postoperative films The average interval between the two postoperative films was eleven months Between the preoperative and the immediate postoperative films there was no increase in volume of the gallbladder in 2 cases and a small increase in 1 case The late postoperative film, compared with the preoperative film, showed definite dilatation of the gallbladder in each case—but less striking than the dilatation after partial gastrectomy The Hollander insulin gastric-secretion test indicated in complete vagal section in each case

Of 15 cases in which a preoperative series of films was followed by at least one postoperative series, the gallbladder became much dilated in 14 In 1 case there was no dilatation in the final radiograph nine months after a routine antecolic partial gastrectomy with spur It can be said, therefore, that dilatation of the gallbladder is an almost consistent change after elective gastric surgery, and that this dilatation was progressive in perhaps half our cases The increase in gallbladder volume was an unexpected finding

The follow-up is being continued to ascertain the duration of this dilatation

The volume of the gallbladder can be computed accurately (Boyden 1928, Siffert de Paula e Silva 1949) The table shows measured gallbladder volumes in 4 of our cases after routine partial gastrectomy without vagotomy

Emptying-rate of Gallbladder After Milk-and-egg Mixture

Partial gastrectomy (*antecolic anastomosis with spur*) —9 cases In 7 cases there was a preoperative and an immediate postoperative series, the emptying-rate was unchanged in 2 cases and increased in 5, the increase was striking in 3 of these 5

In 6 cases there was an immediate and a late postoperative series In the second postoperative series, the emptying-rate was further increased in 4 cases, the increased emptying seen in the immediate postoperative series was maintained in 1 case,

MEASURED GALLBLADDER VOLUME IN THE TWO-HOUR BILIGRAFIN FILM

Case	Sex, age, lesion	Radiograph series	Gallbladder		Comments
			Volume (ml)	Position	
1	F 42 G U	First post-operative Second post-operative (10 months)	18 2 49 7	Normal Unchanged	The gallbladder more than doubled its volume in the 10 months after partial gastrectomy
2	M 56 G U	Preoperative First post-operative	51 2 82 1	Normal Unchanged	Over 50% increase in gallbladder volume after partial gastrectomy
3	M 58 D U	Preoperative First post-operative Second post-operative (9 months)	40 5 83 5 71 8	Normal Lower Lower	The gallbladder doubled its volume after partial gastrectomy No progressive increase
4	M 51 D U	Preoperative First post-operative Second post-operative (10 months)	32 3 40 6 73 7	Normal Unchanged Unchanged	Progressive increase in volume after partial gastrectomy, the final volume being more than double the initial

D U , duodenal ulcer, G U , gastric ulcer The operation in each case was partial gastrectomy, Schoemaker in case 1 and Billroth type II with antecolic anastomosis and spur, in the others

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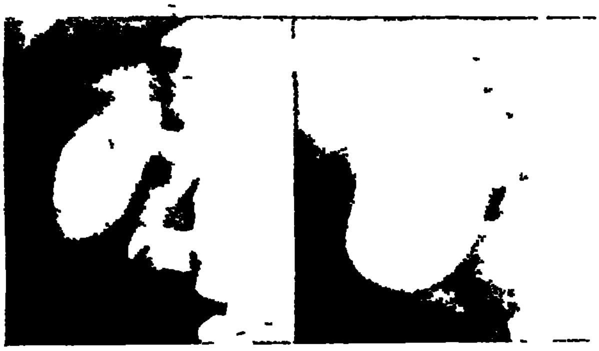
* Based on a paper read before the Manchester Regional Association of Surgeons, June, 1957



(a) (b)

Fig 1—Case 1 Intravenous cholecystogram, 2-hour film (a) 10 days after operation, gallbladder volume 18·2 ml. (b) 10 months later; volume 49·7 ml

and the unchanged rate in the immediate postoperative series remained unchanged in 1 case.

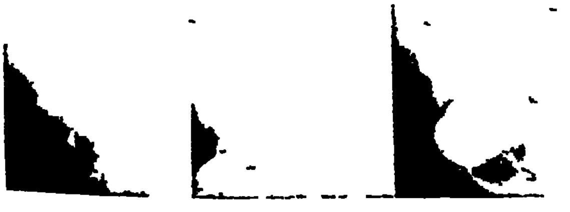
Partial gastrectomy (Schoemaker)—2 cases, with an immediate postoperative and late postoperative series in each. In 1 case in the late postoperative series the rate was increased; in the other there was no change.

Partial gastrectomy and vagotomy—4 cases, with a preoperative and late postoperative series in each case. In 3 cases the emptying-rate was increased and in 1 there was no change.

Vagotomy and posterior gastroenterostomy—3 cases, with three series of films in each. In 1, the emptying-rate was unchanged in both postoperative series. In the remaining 2, the first postoperative series showed no change in 1 case, and a slower emptying-rate in the other. The second postoperative series in each case showed an increase in emptying-rate compared with the preoperative series.

In 15 cases there was an immediate preoperative and one postoperative series, in 11 of these the emptying-rate of the gallbladder was increased after a fatty meal. This increase is mainly limited to the ten-minute and fifteen-minute films, showing that the emptying begins earlier and is more active than before operation. Dilatation of the gallbladder and increase in emptying-rate must be accepted as unrelated changes, because not all gallbladders that are dilated have shown an increase in emptying-rate, and the emptying-rate has increased in undilated gallbladders. No film has shown dilatation of the common duct, at the time of either dilatation or emptying of the gallbladder. There has therefore been no indication at any time of contraction or failure of relaxation of the sphincter at the lower end of the common duct.

The changes in the gallbladder after elective gastric surgery are dilatation, which is often progressive, and an increase in emptying-rate. The gallbladder has apparently moved downwards, by the width of one lumbar vertebra, in 2 cases. The doubling in volume of the gallbladder in 12 days after simple gastrectomy is one of the most striking concomitant physiological changes seen in all abdominal surgery.



(a) (b) (c)

Fig 2—Case 4 Intravenous cholecystogram, 2-hour film. (a) 7 days before operation, gallbladder volume 32·3 ml. (b) 10 days after operation volume 40·6 ml. (c) 10 months after operation, volume 73·7 ml.

Correlation of Changes in the Gallbladder with the Incidence of "Dumping" and Bilious Vomiting

In these 18 patients there has been 1 case of "dumping"—vertigo, leg weakness, and sweats—developing eleven months after partial gastrectomy, and 1 of minor bilious vomiting developing nine months after a Schoemaker partial gastrectomy. This bilious vomiting lasted only two months. In the patient with "dumping" the immediate postoperative film showed that the gallbladder had doubled its size with an increase in emptying-rate. There was no change, however, in the late postoperative film nine months after operation. As the "dumping" developed eleven months after operation, it is almost certain that there were no associated changes in the gallbladder. In the patient with bilious vomiting, the gallbladder had doubled its volume (though it could still actively contract) during the ten months after operation. The bilious vomiting developed nine months after operation, that is, at a time when gallbladder changes were taking place. It is therefore possible that these changes in the gallbladder caused or exaggerated the minor degree of bilious vomiting in this case. But in fully developed bilious vomiting the amount of fluid lost is substantial. It is unlikely that the release of a relatively small additional volume of bile by active contraction of a dilated gallbladder can be a determining factor in the production of striking bilious vomiting.

Discussion

It seems certain that the emptying-rate of the gallbladder depends on that of the stomach. This sequence will account for all the changes in the emptying-rate of the gallbladder reported above after elective gastric surgery. The remaining problem is to explain the dilatation of a gallbladder that has retained its ability to contract.

Fulton (1955) writes

> "When both vagi are cut, the gallbladder responds to the egg-yolk meal in its normal manner, suggesting that in the absence of the parasympathetic innervation the hormonal mechanism is sufficient to cause normal evacuation of the gallbladder."

Johnson and Boyden (1952) conclude that

> 1 Complete severance of the vagi results in progressive enlargement of the gallbladder. They found the fasting volume approximately doubled by complete vagotomy.
>
> 2 The vagi are not essential to evacuation of the human gallbladder, and emptying is regulated primarily through a hormonal mechanism.

It is clear from Mitchell's (1953) diagrams that the vagus supply to the gallbladder runs very close to the left gastric artery, in the cœliac division of the posterior vagus, and in the gastrohepatic omentum. In view of this, it is highly probable that the vagus supply to the gallbladder will be severed once, if not twice, in a routine partial gastrectomy.

Both formal vagotomy and partial gastrectomy therefore produce dilatation of the gallbladder. It seems certain that this dilatation is caused by section of its vagal supply during partial gastrectomy.

In a paper published in December, 1956, when this work was nearly complete, Scott and Whiteside drew attention to the presence of an enlarged gallbladder in 7 cases of postgastrectomy bilious vomiting. No attempt was made to explain this finding It will have been noted that none of our patients had well-established post-gastrectomy bilious vomiting

One additional thought may be committed to paper It seems that, after partial gastrectomy, an excessive amount of cholecystokinin is liberated and causes a very dilated gallbladder to contract to a very small size in ten to fifteen minutes It seems possible that some such active substance, liberated in excess by a fatty meal, may "spill over" into the general circulation and produce the "dumping syndrome" An investigation of the portal stream would throw light on this point

Summary

Gallbladder function after elective gastric surgery has been investigated in 18 patients by means of intravenous cholecystography

The characteristic changes are a dilatation of the gallbladder that is sometimes progressive and an increase in its emptying-rate after a fatty meal

The dilatation is probably caused by section of the vagus nerves, and the emptying-rate of the gallbladder probably depends on that of the stomach

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IMPROVED METHOD OF LABELLING RED CELLS WITH RADIOACTIVE PHOSPHORUS

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When radioactive phosphorus is added to heparinised blood and the mixture is then incubated at 37°C, about 30% of the ^{32}P is incorporated in the red cells during the first hour (Hevesy et al 1944, Reeve and Veall 1949, Wilklander 1956) In the course of experiments on the metabolism of red cells in this laboratory it was found by chance that the uptake of ^{32}P by red cells washed in citrate was very much more rapid than this We report here the results of an investigation of the factors concerned in this rapid uptake and describe an improved method of labelling red cells with ^{32}P

Preparation of Red Cells

Red cells were obtained from blood freshly drawn into a heparinised syringe The blood was transferred to a screw-capped glass container and centrifuged The plasma was taken off into a new container, most of the red cells were sucked up from the bottom of the container so as to leave behind as much as possible of the buffy coat, the red cells were then mixed with their own plasma to give blood poor in white cells 2 ml quantities of this blood were used and, as an approximation, it was taken that each 2 ml contained 1 ml of red cells In some experiments the blood was simply packed by centrifugation and the supernatant fluid was discarded before ^{32}P was added to the packed cells In other experiments the red cells were washed by adding about 20 ml of a wash solution to the 2 ml of blood, after centrifugation the supernatant fluid was discarded and the cells were resuspended by adding 1 ml of one of a series of solutions which were being tested

Radioactive Phosphorus

^{32}P was usually obtained without carrier (P B S 1 from the Radiochemical Centre) and was diluted in 0 9% sodium chloride, to which sodium phosphate was added in a concentration of about 0 1 mg per ml as carrier The volume of solution added to 1 ml of red cells was initially 0 1–0 5 ml During the course of the work it became apparent that sodium chloride interfered with the uptake of phosphorus, therefore the ^{32}P with high specific activity was diluted in the following solution

Trisodium citrate 3 0 g
Sodium di-hydrogen phosphate ($NaH_2PO_4 2H_2O$) 0 015 g
Glucose 0 2 g
Water to 100 ml

This solution, which has a pH of about 6 9, is referred to as citrate-phosphate

The diluted ^{32}P solution used in the uptake experiments contained about 5 μC per ml The ^{32}P solution used for labelling red cells for estimation of the red-cell volume contained about 20 μC per ml

Solutions Used for Washing or Resuspending Erythrocytes

To each of the following solutions, glucose in a concentration of 200 mg per 100 ml was added, but, to save repetition, the presence of glucose in the solutions is not mentioned in referring to them subsequently

Citrate-phosphate —This solution was the one described above

Saline-phosphate —1 0% sodium chloride with 0 015% sodium dihydrogen phosphate (pH 6 8)

Saline —0 9% sodium chloride

Potassium chloride —1 14% KCl (this concentration was chosen as being isotonic with 0 9% NaCl)

Citrate —3 0% trisodium citrate

Citrate-saline —1 0% trisodium citrate in 0 9% NaCl Similarly citrate-KCl was 1 0% trisodium citrate in 1 14% KCl

Sodium sulphate —1 7% anhydrous sodium sulphate

Sucrose —6% sucrose This concentration was chosen because in a lower concentration, such as 4%, the red cells were hæmolysed, and in a higher concentration, such as 10%, they tended to sludge

Sucrose-saline, containing 4% sucrose and 0 6% NaCl, was also tested, in a further experiment 6% sucrose to which 0 1% calcium chloride had been added was also tested (*sucrose with* $CaCl_2$)

E D T A —3% ethylene diamine tetra-acetic acid (disodium salt)

Estimation of Rate of Glycolysis

Fresh red cells from heparinised blood were washed either in citrate-phosphate or in saline-phosphate One volume of cells was then resuspended in an equal volume of the solution in which the cells had been washed, and the mixture was incubated at 37°C for one or two hours The glucose concentration of each mixture was estimated by Nelson's (1944) method before and after incubation The hæmoglobin concentration of the mixtures was also estimated, and from this the packed-cell volume was deduced

Localisation of ^{32}P in Phosphate Compounds of Red Cells

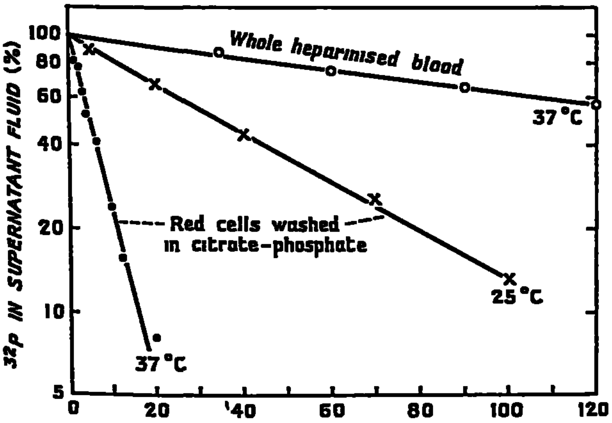
Red cells were washed once in citrate-phosphate and were then incubated with ^{32}P at 37°C for thirty minutes The cells were then washed twice in ice-cold saline The acid-soluble phosphorus compounds were extracted from the cells and fractionated by the method described by Hughes Jones and Robinson (1957) The ^{32}P content of the fractions was also estimated

Estimation of Red-cell Volume

About 20 ml of blood was drawn into a heparinised syringe 10 ml was placed in an empty container, and the other 10 ml was mixed with A C D 3 ml Both samples were spun About 1 ml of red cells was taken from the heparinised sample, the cells were aspirated from the bottom of the container so as to avoid the buffy coat The cells were washed once in 20 ml of citrate-phosphate solution Then to the packed cells was added 2–3 μC of ^{32}P diluted in a volume of

0 1-0 4 ml of citrate-phosphate solution The mixture was placed in a water-bath at 37°C for thirty minutes (fifteen minutes in one experiment) The cells were then washed twice in ice-cold isotonic saline and finally resuspended in about 10 ml of saline solution and added to washed ^{51}Cr-labelled cells (see below)

The sample of blood mixed with A C D was centrifuged and the supernatant fluid discarded To the packed cells about 50 µC of ^{51}Cr was added and well mixed The mixture was left at room temperature for about thirty minutes The cells were then washed twice in saline solution, resuspended in about 10 ml of saline solution and added to the suspension of ^{32}P-labelled cells The mixed suspension of ^{32}P-labelled and ^{51}Cr-labelled cells was then made up to a volume of about 25 ml with saline solution and kept cold until the time of injection 20 ml was injected from a calibrated syringe, and three or four samples of blood were taken from the opposite arm from about ten minutes after injection to about sixty or seventy minutes after injection The packed-cell volume of each sample was determined in duplicate, and the values were corrected for trapped plasma The ^{32}P values, as counts per minute per ml of red cells in each sample, were then plotted on semilogarithmic paper, and the best straight line was fitted to the points by eye From the line the value at 0 minutes was deduced In the case of the ^{51}Cr values it was assumed that there was no significant loss of ^{51}Cr from the circulation during the period of observation, and the ^{51}Cr value was therefore taken as the mean of all the samples expressed in terms of counts per ml



Uptake of ^{32}P in whole heparinised blood compared with uptake by red cells washed in citrate-phosphate (3% citrate with 0 015% sodium dihydrogen phosphate, see text)

Results

The accompanying figure shows the uptake of ^{32}P by red cells washed in citrate-phosphate, compared with the uptake in whole heparinised blood In cells washed in citrate-phosphate, and resuspended in citrate-phosphate, uptake is a simple exponential process with a half-time of five minutes at 37°C, and of thirty-five minutes at 25°C By contrast, in heparinised blood half the ^{32}P is taken up, at 37°C, in two and a half hours The rate of uptake of ^{32}P in red cells washed in citrate-phosphate and left in citrate-phosphate at +4°C is not shown because it was negligible (less than 2% in twenty-four hours)

Some of the results of experiments designed to elucidate the above-mentioned findings are set out in tables I–III, all the experiments were made on at least two separate occasions, and all the results are mean values derived from at least two experiments

When ^{32}P was added directly to packed red cells obtained from heparinised blood, the rate of uptake was considerably increased, thus 79% of ^{32}P was incorporated in the red cells in thirty minutes at 37°C When 0 2 ml of plasma was added to 1 ml of red cells before the ^{32}P was added, the uptake was 42%, the addition of 1 ml of heparinised plasma to 1 ml of red cells reduced the uptake to 12% The addition of 1 ml of 0 9% NaCl to 1 ml of cells reduced the uptake to a similar level On the other hand, the addition of 1 ml of citrate or of citrate-phosphate to 1 ml of cells led to a greatly increased uptake of ^{32}P, the effect of 1% citrate in 0 9% NaCl was intermediate (see table I)

TABLE I—UPTAKE OF ^{32}P BY RED CELLS FROM HEPARINISED BLOOD RESUSPENDED IN VARIOUS SOLUTIONS

Solution added to 1 ml of packed red cells		Uptake of ^{32}P (%)*
Volume (ml)	Composition	
Nil	—	79
0 2	Plasma	42
1 0	"	12
1-0	Saline	10
1 0	Citrate	60
1 0	Citrate-phosphate	57
1 0	Citrate-saline	30

* After 30 minutes at 37°C.

Effect of Washing Red Cells in Citrate-phosphate

In a series of experiments red cells from 2 ml of heparinised blood were washed once in 20 ml of citrate-phosphate solution The supernatant fluid was then removed, and the red cells were resuspended into various solutions, the results are summarised in table II

The addition of ^{32}P to packed red cells washed in citrate-phosphate invariably led to rapid and complete uptake of ^{32}P Thus in eight experiments the average uptake after thirty minutes at 37°C was 98% When 0 5 ml of citrate-phosphate solution was added to the cells before ^{32}P was added, the uptake was slightly reduced, but even after the addition of 1 ml the uptake was still 87% On the other hand, when saline solution was added to the cells, the uptake was greatly reduced, thus the addition of only 0 2 ml of saline solution to 1 ml of cells reduced the uptake to 51%, and the addition of 1 ml reduced the uptake to 11% When citrate-saline rather than saline solution was added, the uptake was almost as poor as in saline solution alone The addition of KCl produced effects indistinguishable from those of NaCl

Red Cells Washed in Other Solutions

When red cells were washed in sodium sulphate, saline, or sucrose-saline and then resuspended in an equal volume of solution, the uptake was 24–34% On the other hand, when red cells were washed in 6% sucrose or in 3% E D T A and then suspended in 0 5 to 1 ml of the same solution, the uptake was very high

TABLE II—UPTAKE OF ^{32}P BY RED CELLS WASHED ONCE IN 20 VOLUMES OF CITRATE-PHOSPHATE SOLUTION AND RESUSPENDED IN VARIOUS SOLUTIONS

Solution added to 1 ml packed red cells		Uptake of ^{32}P (%)*
Volume (ml)	Composition	
Nil	—	98
0 5	Citrate-phosphate	92
1-0	" "	87
0 2	Saline	51
0-4	"	32
0 5	"	22
1-0	"	12
0 5	Citrate-saline	23
1-0	" "	17
0 5	KCl	18
1 0	"	10
0 5 ml	Citrate-KCl	20
1-0 ml	Citrate-KCl	12

* After 30 minutes at 37°C.

TABLE III—UPTAKE OF ^{32}P BY RED CELLS WASHED ONCE IN 20 VOLUMES OF SOLUTION AND RESUSPENDED IN VARIOUS SOLUTIONS

Wash solution	Solution added to 1 *ml* of packed red cells		^{32}P (%) *
	Vol (ml)	Composition	
Sodium sulphate	1 0	Sodium sulphate	28
Saline	Nil	—	74
"	1 0	Saline	27
"	1 0	Citrate	66
Sucrose-saline	Nil	—	73
" "	1 0	Sucrose-saline	24
Sucrose	0 5	Sucrose	98
"	1 0	"	99
"	0 5	Sucrose with $CaCl_2$	98
E D T A	1 0	E D T A	97

* After 30 minutes at 37°C

(97%) The addition of 0 01% $CaCl_2$ to 6% sucrose did not diminish the uptake (see table III)

Rate of Glycolysis

In citrate-phosphate the rate of utilisation of glucose at 37°C was about 30 mg per 100 ml of red cells per hour, and this did not differ significantly from the rate observed in saline-phosphate

Localisation of ^{32}P in Phosphate Compounds Within Red Cells

As described above, cells washed in citrate-phosphate and then incubated with ^{32}P at 37°C were analysed 85% of the ^{32}P was present in the fractions containing adenosine triphosphate and 2 3 diphosphoglycerate The remaining 15% was distributed almost equally between the fractions containing adenosine diphosphate and fructose diphosphate and the fractions containing adenosine monophosphate, inorganic phosphorus, and sugar monophosphates

Rate of Loss of ^{32}P in vitro from Labelled Red Cells

The rate of loss of ^{32}P from red cells labelled by the "new" way (i e , previous washing in citrate-phosphate) was compared with the rate of loss from red cells labelled in the "old" way (simple addition of ^{32}P to heparinised blood) The cells were in each case incubated at 37°C with ^{32}P for thirty minutes, washed twice in ice-cold saline solution, and then resuspended in half their volume of heparinised plasma and reincubated at 37°C The loss from red cells labelled in the new way was a little greater than that from red cells labelled in the old way —e g , after an hour about 8% and 4% respectively

Rate of Loss of ^{32}P in vivo from Labelled Red Cells

Tests were made on seven people 5 healthy volunteers and 2 patients with leukæmia The results are shown in table IV The agreement between the ^{51}Cr results and the results obtained by the "new" method of ^{32}P labelling was extremely close Thus, if the ^{51}Cr value is taken as 100%, the mean ^{32}P value was 100 05%, and the coefficient of variation of the ^{32}P results was 0 9% As table IV also shows, the loss of ^{32}P in the first sixty minutes after injection was 10%

TABLE IV—RESULTS IN VIVO COMPARISON OF ^{32}P LABELLING OF RED CELLS WITH ^{51}CR LABELLING LOSS OF ^{32}P IN 60 MINUTES FOLLOWING INJECTION

Case no	^{32}P counts at 0 min as % of ^{51}Cr counts	^{32}P counts at 60 min as % of ^{32}P counts at 0 min
1	100 0	91
2	101 3	89
3	100 3	91
4	98 9	90
5	99 9	89 5
6	99·0	—
7	100 9	89 5
Mean	100 05	90

Discussion

Although it is usually held that the uptake of phosphate by red cells depends closely on glycolysis, it is clear that the greatly accelerated uptake observed in cells washed in citrate cannot be directly related to an increase in glycolysis Thus, cells washed in citrate take up ^{32}P about thirty times more rapidly than do cells in heparinised plasma, although their rate of glycolysis is not increased Similarly, cells washed in E D T A take up ^{32}P very rapidly, although in such an acid solution glycolysis must be depressed

The results suggest that the most important factor in the acceleration of uptake is the amount of penetrating anion present in relation to the volume of red cells Thus, packed red cells from heparinised blood take up phosphate well, but the addition of only a fifth volume of plasma to the packed red cells reduces the uptake from about 80% to 40%, and red cells suspended in an equal volume of plasma have an uptake of only 12% (all these figures refer to the uptake after thirty minutes' incubation at 37°C) The effect of isotonic saline, potassium chloride, and sodium sulphate solutions is very like that of plasma On the other hand, E D T A has an effect very like that of citrate These latter substances appear to act simply as non-penetrating anions, because sucrose, which is also a substance which does not readily penetrate the red-cell membrane, has the same effect This suggests that anions such as chloride and sulphate normally compete with phosphate for some transport mechanism and that the uptake of phosphate can therefore be improved by any means which reduces the amount of these competing anions in the fluid in which the red cells are suspended

The improvement in uptake produced by citrate cannot be due simply to the binding of calcium, because the uptake is rapid in the presence of physiological amounts of calcium, provided that the concentration of other electrolytes has been reduced by washing (see experiment with sucrose-CaCl in table III)

The fact that the phosphate is firmly incorporated into organic phosphates within the red cell, even when the uptake is very rapid, is shown by the analyses of radioactivity in organic phosphate compounds Similarly, the fact that the uptake is seven times as rapid at 37°C as at 25°C and that it is virtually arrested at +4°C shows that it does not simply depend on diffusion into the red cells but is an active process

Further evidence on this point is supplied by the observation that glycerol in a concentration of about 6 molar inhibits glycolysis and also inhibits the uptake of ^{32}P in red cells previously washed in citrate (Jones et al 1957)

Estimates of red-cell volume by the new rapid uptake method of ^{32}P agreed very closely with simultaneous estimates made with ^{51}Cr The loss of ^{32}P from the red cells during the first hour after injection (10%) hardly differed from that observed after injecting red cells labelled in the usual way (Mollison 1956)

In a previous paper from this laboratory estimates of red-cell volume, using ^{51}Cr and ^{32}P (Reeve and Veall 1949), were made in 14 people The ^{32}P estimates were higher in 8 and lower in only 2 people (Mollison and Veall 1955) It now seems that most of this discrepancy was due to failure to apply a correction to the ^{32}P standards —to take into account the fact that the standards were diluted in water When solutions of radioactive phosphorus are diluted in blood, as they should be for strict comparison with the samples of blood, their counting-rate is about 0 98 times the rate observed when they are diluted in water If this correction factor had been applied to the previous results, the agreement between the ^{32}P and ^{51}Cr results would have been almost exact It remains true, as pointed out in the previous paper, that the ^{32}P method is liable to give overestimates of red-cell volume because of the tendency of ^{32}P to adhere to particles of dust, white cells, bacteria, &c One advantage of the much more rapid uptake obtained when the red cells are first washed in citrate is that virtually all the activity is incorporated in the red cells, and thus errors from injecting ^{32}P attached to other particles is negligible

Summary

When cells are washed once in citrate and are then incubated with radioactive phosphorus at 37°C, the rate of uptake of phosphorus is very rapid, the process having a half-time of about five minutes This acceleration over the rate normally obtained seems to be due to the removal of competing anions, since it is also produced when the red cells are washed in sucrose

Red cells labelled in this way may conveniently be used for estimating the red-cell volume, because the rate of loss of ^{32}P from such labelled red cells is not significantly more rapid, either in vitro or in vivo, than that observed when red cells are labelled in the usual way

This method of labelling is considerably more convenient than that currently in use Not only is it more rapid but also it is more complete, hence the red cells need less washing Very close agreement with simultaneous estimates made by the ^{51}Cr method was observed in 7 cases

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UNILATERAL RENAL INJURY DUE TO TRANSLUMBAR AORTOGRAPHY

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THE risks attending translumbar aortography have recently been discussed (*Lancet* 1957, Trippel et al 1957) and the major complications reviewed (Crawford et al 1957) The renal complications of aortography have received considerable attention, and ten deaths from renal failure have been reported by Crawford et al (1957) and Conger et al (1957) Crawford et al consider renal injury to be the commonest significant complication and refer to 12 cases of unilateral renal damage, adding a further personal case There are few reports in British literature on renal complications following aortography Riches (1955) mentions a case of renal failure with recovery, and Roy (1957) and Dormandy et al (1957) give details of 2 further cases The following case is reported because severe unilateral renal damage was sustained which was entirely asymptomatic

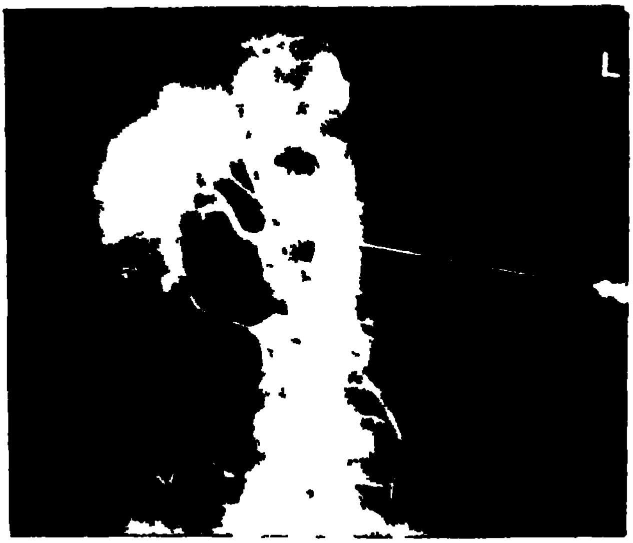

Fig 1—Needle has entered lumen of right renal artery, tip of needle lying at mouth of arterial branch to upper pole Aberrant renal artery supplies lower pole

Case-report

A merchant seaman, aged 64, was admitted to hospital on May 7, 1957, with seven years' history of intermittent claudication affecting his right leg At first confined to his calf it had recently spread to his thigh, exercise tolerance being limited to about 50 yards His foot felt cold and numb, but he had not noted any change in its colour His past medical history was not significant, he had smoked twenty cigarettes a day since adolescence

On examination he was well built, healthy-looking, and inclined to obesity His heart was normal clinically, his blood-pressure 145/85 mm Hg, and his radial pulse regular, with some thickening of the vessel wall All peripheral pulses, including the femoral, were absent from his right leg, and only the dorsalis pedis artery was impalpable in his left leg Thrombosis of either his right common iliac artery or his right external iliac artery was diagnosed

Translumbar aortography was done on May 8, 1957, under thiopentone anæsthesia 50 ml of 70% sodium acetrizoate ('Diaginol') was injected by the one-needle technique using a mechanical pressure apparatus The aortogram is shown in fig 1 The contrast medium had been injected directly into the right renal artery, and the aorta filled by overflow Occlusion of the right common iliac artery and part of the external iliac artery was confirmed The distal part of the external iliac artery and the femoral artery were patent

Progress—After aortography the patient's urine was examined daily, but no abnormal constituents were found, and its specific gravity varied from 1 018 to 1 024 There were no symptoms or signs of injury to the right kidney The output of urine was never less than 800 ml in twenty-four hours, and the blood-urea level was 40 mg per 100 ml Although there was no positive evidence of renal damage, it seemed advisable to postpone intravenous urography rather than subject the kidneys to further exposure to organic iodide The patient was discharged on May 14, there being no suitable homograft then available

Readmission—He was readmitted on June 10, and intravenous pyelography was done, which showed a normal left kidney but poor concentration in the right (fig 2) The urine did not contain albumin, cells, or casts, and its specific gravity was 1 022 The blood-urea level was 41 mg per 100 ml and the blood-pressure 146/80 mm Hg Next day an aortofemoral shunt homograft was inserted to bypass the thrombosed segment Postoperatively the posterior tibial pulse became palpable and has remained so The patient was discharged from hospital on June 30

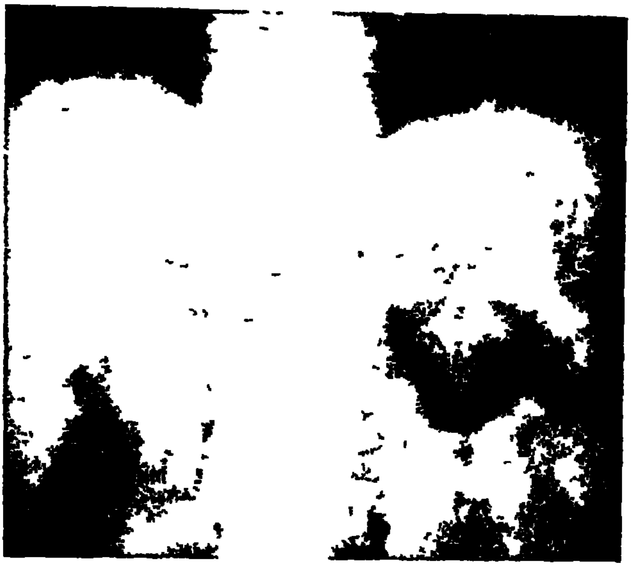

Fig 2—Renal function impaired on right side

Follow-up —On Oct 5 the ureters were catheterised, and indigo-carmine was injected intravenously The dye appeared from the left ureter after six minutes and showed good concentration at the end of an hour On the right side there was no obvious excretion of dye at this time The patient was in good health, and the graft was functioning The blood-urea level was 38 mg per 100 ml

Discussion

The present case illustrates one of the well-recognised complications of aortography and is of special interest in view of the absence of clinical manifestations If the implications of direct injection of organic iodide into the renal artery had not been appreciated, the lesion would possibly have gone unrecognised

In 5 of the 13 published cases of unilateral renal injury complete recovery apparently took place, the 8 others showing either no function or reduced function In the first case an unstated volume of sodium iodide was accidentally injected into the left renal artery, this was followed by pain in the left loin for forty-eight hours, but subsequently phenolsulphonephthalein was excreted normally by the left kidney (Melick and Vitt 1948) In all the other cases the injury was to the right kidney, which is anatomically more susceptible to damage

The factors responsible for renal damage in aortography are considered to be misdirection of the needle, multiple injections, excessive pressure or volume, drug sensitivity, or a combination of two or more of these factors (Miller et al 1954) In all the unilateral cases the needle has been directed toward the origin of the renal artery or has lain within its lumen This hazard is avoidable if the practice of making "scout" injections is adopted as a standard part of the procedure Multiple injections are to be avoided, particularly repeated aortic punctures, as shown by Crawford et al (1957) All the cases of serious hæmorrhage following aortography have been associated with multiple aortic punctures or change in position of the patient with the needle still in place

The use of mechanical apparatus to inject contrast media under pressure has received considerable criticism Many clinics obtain satisfactory films by manual pressure only, and in view of the dangers of aortic dissection, emphasised by Gaylis and Laws (1956), it seems advisable to abandon this technique

Toxicity and idiosyncrasy are difficult to assess Iodism does not appear to be a serious problem, and there have been no deaths from anaphylaxis Organic iodides, however, are harmful in another way, either by destroying tissue directly or by producing ischæmia, and the dosage, concentration, and type of compound responsible for this seem to vary As little as 15 ml of 70% solution of sodium acetrizoate ('Urokon') has been known to impair renal function (McAfee and Willson 1956) and was the medium used in 12 of the cases of unilateral lesions and in many of the bilateral cases

Goodwin (1957) has therefore abandoned sodium acetrizoate in favour of 50% sodium iodomethamate U S P ('Neo-iopax'), although it has been responsible for 1 death (Josselson and Kaplan 1954), and 1 case of unilateral renal injury (Harvard 1953)

80% sodium iodide, so notorious as a cause of death from thrombosis of the superior mesenteric artery in aortography, has been injected directly into the right renal artery without apparent effect (Maluf and McCoy 1955), but a patient cited by Crawford et al (1957) died of bilateral renal injury following the injection of only 15 ml of sodium iodide Idbohm (1956) considers that the use of sodium iodide in renal angiography is unjustifiable

The tolerance to other iodine compounds varies widely from one person to another, and the concentration of the drug is important in this respect (Idbohm and Berg 1954), as well as the type of compound used

So far as renal angiography is concerned, the techniques of selective angiography described by Ödman (1956), Edholm and Seldinger (1956), Tillander (1956) and Gregg et al (1957) seem to offer a measure of safety, but translumbar aortography, still necessary in the investigation of peripheral vascular disease, probably requires a safer contrast medium than is at present available

Summary

A case of unilateral renal injury following translumbar aortography is reported

There was no clinical indication of renal damage

The factors responsible for this lesion are discussed, and the conclusion is drawn that a safer contrast medium is required

I am grateful to Mr G G Bruce for permission to publish, and to Mr G E Mavor for his criticism and advice

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CARDIAC SYNCOPE AFTER SWALLOWING

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THIS report describes a patient who had many attacks of cardiac syncope immediately after swallowing food or fluids. A midœsophageal diverticulum was found. Two descriptions of similar cases have been published (Weiss and Ferris 1934, Correll and Lindert 1949), but the syndrome is rare and interesting enough to merit a third.

Case-report

In October, 1955, a lorry driver, aged 58, had pain in his chest while loading a lorry. The pain passed off with rest but recurred two days later. On each of the three following days it came on while he was at rest, it was severe and accompanied by vomiting, and each attack lasted progressively longer, until finally pain persisted all night.

On admission to hospital on Oct. 11, 1955, short of breath and cyanosed, he showed signs of heart-failure his pulse-rate was 120, pulse regular, and blood-pressure 95/70 mm. Hg. Loud pericardial friction was heard. Electrocardiography showed an extensive transmural anterior myocardial infarct. Radiography of his chest showed that his heart was enlarged.

Treatment and progress.—He was given digitalis, mersalyl, and anticoagulants and improved steadily. Ventricular extrasystoles appeared and were sometimes numerous. Thirteen days after admission, while being fed with a breakfast of boiled egg, he suddenly fell back unconscious on his pillow, he threw his arms outwards, and his eyes turned up. He recovered in about a minute. Questioned afterwards, he remembered having had a short attack of unconsciousness forty years before, which he thought had occurred while he was at lunch. Otherwise his convalescence was uneventful. He was discharged on Nov. 21, 1955, free from heart-failure and still taking digitalis folia gr. 1 daily.

Readmission.—In August, 1957, he was sent for consultation because of attacks of fainting. These had started soon after his discharge from hospital, at first they had been infrequent but latterly almost daily. Without exception they had come on while he was either eating or drinking. They were slightly less common with liquids than with solid food, and it made no difference whether the food was hot or cold. His wife said that she had come to be afraid to put food before him. Immediately after swallowing he would feel discomfort which began behind the lower end of his sternum, and seemed to rise towards his throat. Sometimes he would feel faint without losing consciousness, in a more severe attack he would suddenly become unconscious. His wife said that at the beginning of the attack his face would become pale, while he was unconscious his eyes turned up, and he might have a convulsion sufficiently violent to knock the meal off the table. Sudden flushing of the face heralded his return to consciousness. The attacks lasted from one to five minutes, tending to last longer as time passed. Apart from these attacks the patient had been well, was no longer breathless, and had no pain in his chest. He was still taking digitalis.

On examination there were no signs of heart-failure, his pulse-rate was 72, and pulse regular, a soft systolic murmur was heard at the apex, and his blood-pressure was 120/80 mm. Hg. Pressure on either carotid sinus slowed the pulse but caused no faintness. Electrocardiography showed inverted T waves in leads S_1, aVL, and V_3—presumably a sequela of the infarction. There was sinus rhythm except for rare multifocal ventricular extrasystoles, the P-R interval was 0.14 sec. Pressure on either carotid sinus slowed the pulse-rate from 75 to 45 per min. and caused the P wave in the only lead examined (SIII) to become biphasic, the P-R interval was not altered. The effect of drinking cold water for about 5 seconds was then observed three times. The first drink caused asystole lasting 5.6 seconds. This was preceded by three beats in which no P waves were visible in the tracing, which was somewhat disturbed by the activity of drinking. The ventricular complexes were unchanged. At the end of the asystole six beats passed before the P waves reappeared, and of these the second was a ventricular extrasystole. The second and third drinks produced changes similar to those caused by sinus pressure, the heart beat did not again stop. Radiography of the chest showed only slight cardiac enlargement. A barium swallow showed a traction diverticulum of the œsophagus at the level of the bifurcation of the trachea (fig. 1).

Treatment and progress.—The digitalis was stopped, and the patient was given ephedrine, gr. 1/2 t.d.s. During the subsequent eight weeks he had no attacks of fainting, although he sometimes had momentary discomfort in his chest while eating.

Investigation with balloon.—An observation was made (after stopping the ephedrine for two days) in which a balloon 6.3 cm. long and 3.4 cm. in diameter was placed in the œsophagus, inflation of it with 20–30 ml. of air caused, in severe form, the same retrosternal discomfort which initiated his attacks of fainting. With the balloon at the level of the diverticulum the first inflation caused heart-block for three beats, slowing the auricular rate from 88 to 52 without altering the P waves (fig. 2). A second inflation caused heart-block for two beats. The balloon was then moved to a point 4 inches below the diverticulum, the position being checked radioscopically. The first inflation at this site caused heart-block for one beat, followed by a lengthening of P-R interval for three beats, a second inflation only slowed the rate. The balloon was then inflated ten times at the lower site and five times at the level of the diverticulum, the heart beat being observed by auscultation, each inflation slowed the rate, but there were no missed beats.

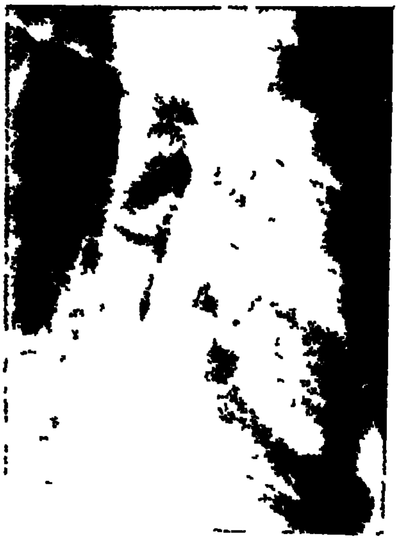

Fig. 1—Barium swallow, showing traction diverticulum of œsophagus at level of tracheal bifurcation.

Discussion

Except that his attacks (with one possible exception) followed a myocardial infarction, this patient closely

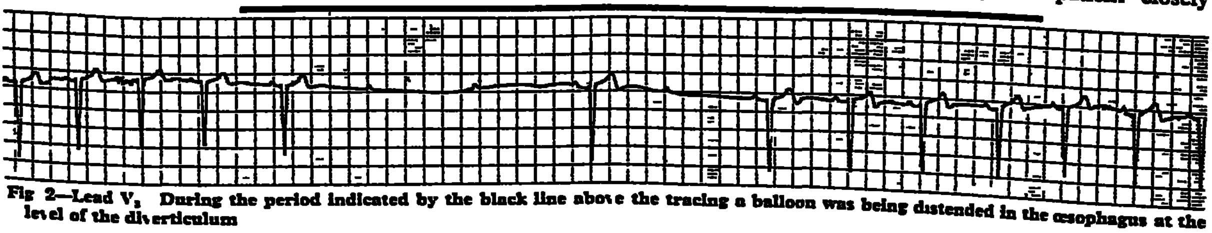

Fig. 2—Lead V_3. During the period indicated by the black line above the tracing a balloon was being distended in the œsophagus at the level of the diverticulum.

resembles those described by Weiss and Ferris (1934) and Correll and Lindert (1949) The œsophageal diverticulum presumably causes the attacks by becoming distended with food and drink, although it has not been shown either in the present patient or in those cited that such distension is the stimulus Weiss and Ferris showed that blocking the vagi in the neck abolished the cardiac response to œsophageal distension, therefore the response was not due to stimulation of motor vagal fibres

In the present patient œsophageal distension did not always cause the same disturbance of conduction Sometimes sinu-auricular block resulted and sometimes auriculo-ventricular block, either change could cause ventricular standstill The change in shape of the P waves during drinking was presumably due to a shift of the pacemaker, a similar effect was observed by Correll and Lindert

A further question is why the attacks started after the myocardial infarction This lesion may have altered the sensitivity of the cardiac impulse to vagal control, or made ventricular escape more difficult A more likely explanation is that the heart was sensitised by digitalis Correll's and Lindert's patient started having attacks eight months after being digitalised, and it was no longer possible to produce faintness by distending the œsophagus after stopping digitalis

The description by Adams and Stokes of fainting attacks accompanied by slowness of the pulse were antedated by three others

Thomas Spens (1793) reported a man, aged 54, who had had three attacks of unconsciousness and whose pulse-rate was 24 The patient had further attacks, one while drinking an infusion of camomile, and one after taking 30 drops of spiritus ammoniæ aromaticus in 2 oz of water Later, feeling better, the patient sat down to dinner

> " upon taking some broth, he almost instantly felt faint, and had the same most distressing sensation as if one of his former fits were coming on The same circumstances took place twice afterwards, on his attempting to swallow something solid About eight in the evening, wishing again to try what would be the effect of swallowing while I was present, he took a bit of newly toasted bread But he had no sooner smelt it, than he felt some of the sensations of a beginning fit, and as soon as he had tasted it he almost instantly cried out, and fell back senseless, with smart convulsions of all his muscles He apparently recovered, however, in a few seconds, but hardly any pulse could be felt for a good many seconds "

He died two days later

> " the body was opened by Mr Fyfe, and, upon the most careful examination, no morbid appearance, of any consequence, could be discovered, either in the thorax or abdomen "

One does not know whether Mr Fyfe would have regarded an œsophageal diverticulum as of any consequence

Summary

A patient is described who had many attacks of cardiac syncope while eating or drinking, he had an œsophageal diverticulum

The attacks ceased when the digitalis which he was having was stopped and he was given ephedrine

Making him drink water and, alternatively, distending a balloon in his œsophagus caused heart-block and ventricular standstill

Previously reported cases are mentioned

I am grateful to Dr A S Bligh for the radiological investigation, Mr R Marshall for the photographs, and Prof Harold Scarborough for advice

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THE AIRWAY IN TONSILLECTOMY

A TECHNIQUE FOR CHILDREN

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Last year Doughty (1957) described a modification of the tongue-plate of the Boyle-Davis gag which allows oral intubation for tonsillectomy in children We had been using a similar technique with standard apparatus, and we here describe how a satisfactory airway can be maintained through an orotracheal tube lying unseen beneath the tongue-plate of an ordinary Boyle-Davis gag

Careful attention to certain details is necessary

(i) An ordinary Magill tube *fitted with a Magill's nasal* connecting-piece is passed through the mouth and is fixed carefully in the midline by strapping immediately below the lower lip It is then connected to the anæsthetic apparatus in the usual way

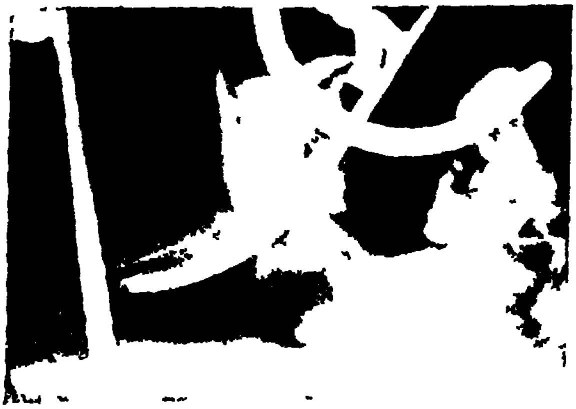

Fig 1

(ii) The Boyle-Davis gag is now introduced, the tube and tongue being retained in the midline as in Doughty's method

(iii) The gag may now be opened as wide as the surgeon requires, the tube lying unseen in the field of operation

(iv) The distal end of the gag is supported by any available mechanical means, but it must not be raised excessively or the tube will be kinked where it emerges from under the tongue-

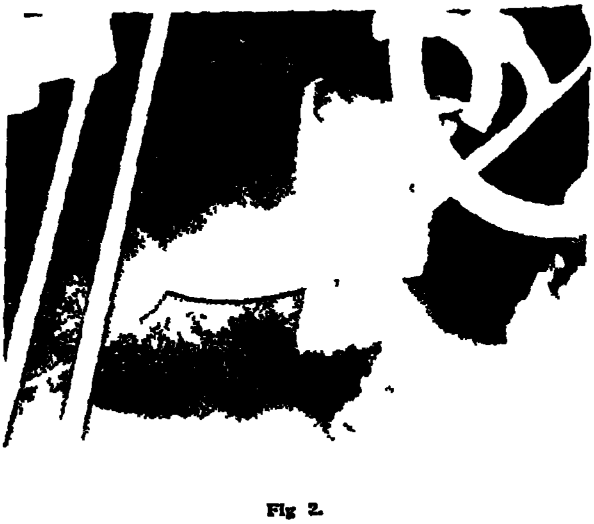

Fig 2

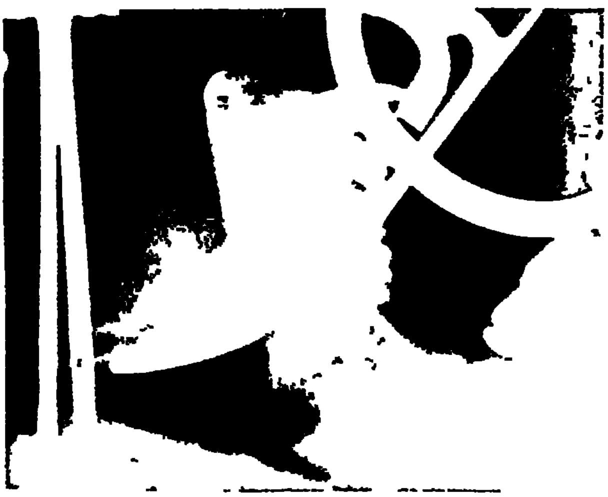

Fig 3

plate to enter the larynx One great advantage of this is tha the pillars of the fauces are thus relaxed, thereby aiding the surgical dissection

Fig 1 shows an ordinary Magill tube actually in use Despite a faint dent in the orotracheal tube *beyond the tip* of the tongue-plate, respiratory sounds were normal and chest movements free and unobstructed Fig 2 shows the effect of raising the tongue-plate hook too far and the mechanism of obstruction thus deliberately caused Obstruction does *not* occur between tongue and plate Fig 3 shows a McIntosh-Oxford tube in use This has a more sturdy wall and is perhaps to be preferred for this technique, though not essential

With colleagues, we have now used this method routinely for all children up to 14 years old without incident and with complete success It has all the advantages of intubation, but the surgeon is unaware of the presence of a tube in his field of operation One of us (K R), who has used the method both with the standard tongue-plate and with the slotted tongue-plate, has found the results equally satisfactory with either

Our thanks are due to Dr J V I Young for suggestions, to the radiological department of Poplar Hospital, for taking the films, and to Mr D Kemp, of the Institute for Diseases for the Chest, for the prints

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Preliminary Communication

LIPOPROTEIN-BOUND CHOLESTEROL IN HÆMOPHILIC SERUM

POSSIBLE ætiological factors in atherosclerosis are intravascular coagulation of blood [1] and alterations in the blood lipids, particularly in the lipoprotein fractions of plasma and their bound cholesterol [2,3] An increase in the amount of total cholesterol in the serum with an increase in the cholesterol content of the β-lipoprotein appears to be commonly associated with developed atherosclerosis, these parameters may be an indication of the state of the arterial tree It is therefore of interest to know whether there is any deviation from the normal cholesterol-lipoprotein pattern in the serum in persons with inherited or congenital deficiencies of blood coagulation such as hæmophilia Information on the occurrence and extent of atherosclerosis or cholesterol-lipoprotein abnormalities in such people is scanty Stewart and Acheson [4] reported the finding at necropsy of severe atherosclerotic changes in an elderly hæmophiliac and gave values for the total and lipoprotein-bound cholesterol

I report here the results of an investigation into the cholesterol content of the α and β lipoproteins of serum in a group of hæmophiliacs and compare them with similar observations in healthy people examined concurrently

MATERIAL

The healthy people were men aged 19–50 (mostly 20–30)

The hæmophiliacs were all men with moderate to severe disease and aged 21–68 (see accompanying table) The clinical diagnosis was confirmed and the type (hæmophilia A or B) determined by finding a blood thromboplastic defect due to a deficiency of either antihæmophilic globulin (hæmophilia A) or Christmas factor (hæmophilia B)

METHODS

Thromboplastin formation was measured by the method of Biggs and Douglas [5] with the additional modification of Bell and Alton [6]

Collection of Serum—Blood was aspirated from an antecubital vein and allowed to clot in a dry glass tube at 37°C for several hours The serum was then separated and either analysed on the same day or stored at −25°C for periods up to several months before being analysed

Analysis of Serum—The lipoproteins were separated by paper electrophoresis, and the cholesterol contents of the α and β lipoprotein fractions were determined by a slight modification of the method described by Boyd [7] Total cholesterol was taken as the sum of the α and β lipoprotein-bound cholesterol The observed cholesterol concentrations were probably somewhat lower than the true values because it was unlikely that the cholesterol was completely extracted from the electrophoretic strip

RESULTS

Healthy people—In 26 men the mean total cholesterol was 173 mg per 100 ml (range 75–272, standard error of the mean ±9 5) The mean percentage cholesterol bound to the β-lipoprotein was 78 2 (range 66/89, standard error of the mean ±0 5)

Hæmophiliacs—The individual data are shown in the accompanying table The mean total cholesterol was 134 mg per 100 ml (range 78–159, standard error of the mean ±7 6) The mean percentage cholesterol bound to the β-lipoprotein was 75 6 mg per 100 ml (range 64–85, standard error of the mean ±2 2)

AGE, TYPE, SERUM-TOTAL-CHOLESTEROL, AND PERCENTAGE CHOLESTEROL IN THE β-LIPOPROTEIN IN 9 HAEMOPHILIACS

Case no	Age (yr)	Hæmophilia type	Total cholesterol (mg per 100 ml)	% cholesterol in β-lipoprotein
1	21	B	124	77
2	22	A	78	70
3	24	B	153	82
4	29	B	131	64
5	29	B	154	77
6	30	A	128	72
7	46	A	153	73
8	48	A	125	80
9	68	A	159	85

The total cholesterol values of the two groups were statistically different (p < 0 05 > 0 01) There was no significant difference between the values for the percentage cholesterol bound to the β-lipoprotein ($p > 0\ 05$)

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[1] Duguid, J B *Brit med Bull* 1955 11, 36

[2] Gofman, J W Glazier, F, Tamplin, A, Strisower, B, De Lalla, O *Physiol Rev* 1954, 34 589

[3] Jencks W P Hyatt, M R Jetton M R., Mattingly, D W, Durrum, E L *J clin Invest* 1956 35, 980

[4] Stewart J W Acheson E D *Lancet*, 1957, i 1121

[5] Biggs R. Douglas, A S *J clin Path* 1953, 6, 23

[6] Bell, W N, Alton, H G *Nature Lond* 1954 174 880

[7] Boyd G S *Biochem J* 1954, 58, 680

DISCUSSION

The significantly lower mean cholesterol level in the hæmophiliacs may be a fundamental difference and related in some way to the disturbance of coagulation However, since an early age these patients have had numerous episodes of bleeding with severe physical stresses and probably poor dietary intake during these periods The difference may therefore merely reflect the direct and indirect effects of recurrent loss of blood with frequent periods of ill health resulting from the nature of the disease In contrast, the percentage distribution of the cholesterol in the α and β lipoproteins showed no significant difference between the two groups The values for both the total and the β-lipoprotein-bound cholesterol in the serum appear to be above the normal range in the atherosclerotic hæmophiliac reported by Stewart and Acheson[4] None of the present hæmophiliacs had symptoms suggesting coronary-artery disease or vascular insufficiency elsewhere X-ray examination of the aorta in the 3 oldest hæmophiliacs did not reveal calcification, this negative finding does not, of course, exclude the possibility of underlying atherosclerotic changes

The data obtained in this study do not necessarily mean that the hæmophiliacs are less disposed to the development of atherosclerosis or possess less of it than do members of a healthy group comparable in age and sex Accurate correlation can only come from direct examination of the arterial tree Nevertheless the present information may be of some value when more pathological evidence is available and other, perhaps larger, series are reported from other sources

The predictive value for atherosclerosis of the amount and distribution of cholesterol in the lipoprotein fractions of serum has still to be assessed Furthermore intravascular coagulation of blood may be independently related to the development of atherosclerosis

SUMMARY

The amounts of total and lipoprotein-bound cholesterol in the serum were determined in healthy people and in hæmophiliacs

The mean total-cholesterol level in the hæmophiliacs (134 mg per 100 ml) was significantly lower than that in the healthy people (173 mg per 100 ml) The percentage cholesterol in the β-lipoprotein of the hæmophiliacs (75 6) was not significantly different from that of the healthy people (78 2)

I wish to thank Prof J S Mitchell, F R S , *for facilities for this work, and Miss Sheila Tomlin for technical assistance The work was done during the tenure of an Elmore Research Studentship*

Department of Medicine,
University of Cambridge

P Barkhan
M D W'srand, PH D Cantab

Medical Societies

THE HEBERDEN SOCIETY

At a meeting of the society on Feb 14, three papers were presented

A New Phenylbutazone Analogue

Dr D M **Burley** had compared phenylbutazone with its metabolite *p*-hydroxyphenylbutazone (designated G27202), which had been reported to have a similar antirheumatic, but more potent uricosuric, effect than phenylbutazone itself G27202 had been substituted for phenylbutazone dose for dose (usually 200–400 mg daily) for from five days to several weeks, in 72 patients with rheumatoid arthritis and ankylosing spondylitis In relief of pain 9 patients found G27202 more effective, and 23 found phenylbutazone more effective, 18 patients considered them equally effective, and 22 found neither effective or the effects variable 56 patients had no gastric intolerance to either compound, and 16 had intolerance to phenylbutazone, of these 16 patients, 8 were intolerant to G27202, but only slightly in 4 G27202 was less effective than phenylbutazone in relieving pain and stiffness in these conditions, but had about half the gastric toxicity

Uricosuric Agents in Gout

Dr G D **Kersley**, Dr E R **Crook**, and Dr D C J **Davey** (Bath) had investigated the effects of G28315, a phenylbutazone analogue, on the clinical condition, urinary uric-acid excretion, and serum-uric-acid levels of 15 patients with typical gout In the 13 with normal renal function the average daily urinary excretion of uric acid rose from 551 mg to 880 mg on a daily dose of 400 mg of G28315, 5 were given 800 mg daily, and in them the daily excretion rose to 1042 mg The average level of the serum-uric-acid fell from 7 8 to 4 0 mg per 100 ml (After 1–1 5 g of probenecid daily the average serum-uric-acid levels fell from 7 8 to 5 2 mg per 100 ml) The response to G28315 in the 2 with impaired renal function was also very satisfactory Intermittent administration for three days in each week did not maintain the lowered serum-uric-acid level No toxic effects were observed on continuous administration of G28315 for periods of four to fourteen weeks, and longstanding joint swellings regressed Acute gouty attacks increased in frequency during the first six weeks, but thereafter these became mild and infrequent, they were promptly terminated by phenylbutazone in all cases The addition of aspirin 3 5 g daily reversed the effects of G28315, and the urinary uric-acid excretion fell below, and the serum-uric-acid level rose above, the control levels

Rheumatoid Polyarthritis with Negative Agglutination Test

Dr A St J **Dixon** had studied all inpatients of the Rheumatism Research Centre at the Manchester Royal Infirmary who had active and progressive polyarthritis with an increased erythrocyte-sedimentation rate and negative sheep-cell agglutination test (S C A T), and in whom no diagnosis was made relevant to the polyarthritis except rheumatoid arthritis (R A)

Of 64 such patients 6 had died and 51 were seen again after an average of five years, when 13 had developed a positive S C A T—of whom most had a distribution of arthritis typical of R A , and half had developed nodules 18 had typical R A and a negative S C A T , none of these had subcutaneous nodules but most of them had flexor-tendon lesions in the hands 15 had an atypical distribution of arthritis and negative S C A T without nodules or flexor-tendon lesions of any sort 11 patients had developed confirmed or probable polyarthritic diseases other than R A including psoriatic arthritis, reticulohistiocytosis, myelomatosis, generalised osteoarthritis, and gout

Dr Dixon concluded that (1) other diseases may simulate rheumatoid arthritis very closely and a negative S C A T may alone indicate the difference, (2) there is a group of patients, requiring further study, with severe polyarthritis which does not fit the clinical and serological picture of R A , (3) a negative S C A T is compatible with severe or fatal disease in otherwise typical R A , and (4) no difference in prognosis was found in patients with typical R A between those whose S C A T was initially negative and later positive, and those in whom the S C A T was negative throughout It was among the 15 cases with a negative S C A T , who also had atypical R A , that some of the severest illnesses and most dramatic remissions were found

Reviews of Books

Modern Trends in Gastro-enterology

Editor F AVERY JONES, M D, F R C P, physician, Central Middlesex Hospital, and consultant in gastroenterology to St Mark's Hospital, and to the Royal Navy London Butterworth 1958 Pp 439 78*s* 6*d*

THE second series appears five years after the first, under the same able editorship The first volume gave a remarkably wide and clear review of most aspects of gastroenterology the second is complementary to the first, but the editor has this time aimed at picking out only certain growing points of the subject, large or small, where advances or new knowledge have been achieved It is thus a book more for the specialist than the general practitioner, but is none the less valuable and important for that indeed, it is exactly the type of collected information that is badly needed

Dr Avery Jones has gathered a team of 39 authors, most of whom are engaged in research on the subjects about which they write Most belong to the younger school of scientists or clinicians in this country, but Dr Jan Waldenström, of Sweden, contributes a fine article on carcinoid, and six of the authors are distinguished physicians from North America Of new work, that on the blind-loop syndrome (Dr John Badenoch) and on the metabolic effects of intestinal resection (Dr W P U Jackson) make fascinating reading, and so does the account by Dr Sheila Sherlock of hepatic coma and liver-failure Ulcerative colitis receives a full discussion which brings together much material and differing opinions on this difficult disease, but it is clear that no fundamental advance has yet been made towards solving its ætiology

Some rarities rightly receive attention, such as the Peutz-Jeghers syndrome, but for the most part this book deals in a clear and practical way with the main aspects of modern gastroenterology, clinical, pathological, radiological, or chemical It deserves a warm welcome and its editor and authors are to be congratulated on a splendid achievement

Atlas of Clinical Endocrinology

H LISSER, M D, clinical professor emeritus of medicine and endocrinology, ROBERTO F ESCAMILLA, M D, clinical professor of medicine, University of California School of Medicine, San Francisco St Louis C V Mosby London Henry Kimpton 1957 Pp 476 £7

MANY endocrine disorders need pictures to describe them effectively here each condition is illustrated by clinical photographs, sometimes in series, showing the evolution of the disease and the results of treatment Radiographs, electrocardiograms, pathological specimens, graphs, or genealogical tables are often included in the same photographic plate The quality of the reproductions is generally satisfactory but not outstanding (the colour plates of Addison's disease and Cushing's syndrome could be improved) The text, in table form, is on the whole comprehensive and accurate Physiological and chemical aspects of the subject are deliberately omitted, which is a pity perhaps, now that clinical endocrinology has the status of an applied science

The section on hypopituitarism suffers from too much classification into different types, and cachexia is overemphasised as a feature of the disease It is not clear that some of the patients depicted have not in fact anorexia nervosa or functional hypothalamic disturbance Elsewhere there are points of emphasis or omissions that might be corrected Distinction is not clearly drawn between sporadic cretinism and childhood myxœdema, and epiphyseal dysgenesis is not mentioned, with thyroid disorders The section on treatment of adrenal crisis does not refer to the use of intramuscular cortisone acetate as a depot or to tapering of dosage The account of phæochromocytoma omits sweating as a cardinal symptom and erroneously describes flushing (instead of pallor) in the attacks The discussion of the pathogenesis of congenital adrenal hyperplasia is not up to date, and the essential failure of testicular maturation is not brought out

The sections on gonadal disorders are probably the best in the book, though the chapter on the undescended testicle does not emphasise the distinction between failure of the spermatic cords to lengthen and the migration of the testes into ectopic situations—the management of these types being fundamentally different The book ends with a section on miscellaneous non-endocrine disorders, and a useful appendix containing growth curves and tables of height-weight-age, bone-age, and dental age

Human Histology

A Textbook in Outline Form LESLIE BRAINERD AREY, PH D, SC D, professor emeritus of anatomy, Northwestern University, Illinois Philadelphia and London W B Saunders 1957 Pp 337 45*s* 6*d*

IN an interesting preface, Professor Arey explains to some extent the sense of disappointment and disagreement which the text will evoke in some readers There are no illustrations, and the style is as terse as a series of memoranda, whose relative importance is marked by varying degrees of indenting the book is, in fact, a derivative of duplicated sheets of typescript As its author claims, " What may, perforce, be lost in smoothness and grace of style is offset by Baedeker-like concision and force and, it may be hoped, clarity " These hopes are fully realised, but it should not be overlooked that Baedeker-like books inform rather than develop comprehension No doubt Professor Arey supplied other elements than mere information in his courses, but without an assurance of this in other places we hesitate to recommend his largely descriptive catalogue of the tissues of the body, for all its immense collection of information

It is disappointing to find that it is still necessary to devote 337 pages to an " outline " of histology Since each " fact " is stated, as far as possible, in a line of the text, which averages 30–40 lines in each page, about 12,000 " facts " receive mention Can the average student absorb more than a portion of all this ? And which portion ?

Deliberate jettison of all that makes a textbook more than a concatenation of statements may be justified if the abbreviation is a true one, and permits more leisure for mental digestion But if compression merely allows the introduction of further pabulum, the meal becomes indigestible In much medical teaching today, mere instruction predominates and education lags behind It would be harsh to judge it entirely in this light, but the book seems to us to have defects as a sole guide to beginners in histology, however useful it may prove to those who, with a background of understanding, seek to revise its facts

Portal Hypertension

ALAN HENDERSON HUNT, D M, M CHIR, F R C S, surgeon, St Bartholomew's and The Royal Marsden Hospital Edinburgh and London E & S Livingstone 1958 Pp 230 40*s*

IN British surgical literature Jacksonian prize essays form an ancient lineage Mr Hunt's monograph on portal hypertension, which was awarded this prize by the Royal College of Surgeons of England in 1956, now appears in print, and it proves him worthy of his illustrious predecessors The book is essentially a clinical account, based on 250 cases, the largest individual series yet analysed in this country It does more, however, than describe methods and present results it reflects the struggles, failures, and successes which have made the first ten years of operative treatment of portal hypertension one of the most exciting chapters in surgery Its smallness was dictated by the requirements of the prize for which it was submitted, and the author regrets that 75,000 words did not allow him to summarise all recent scientific work on liver disease and hepatic circulation, but he has been outstandingly successful in relating that work to his own clinical experience

His concise yet uncramped style, as well as the soundness of his judgment, will assure for the book a warm welcome not only from specialists but also from general physicians and surgeons, many of whom still regard the surgical treatment of portal hypertension with a mixture of awe and distrust If, after reading these pages, they decide that it is still a highly specialised subject, they will yet have enjoyed and profited by a lucid account of a complex but not uncommon group of illnesses

In common with most workers in America and in this country, Mr Hunt favours shunt operations as the surgical treatment, but he never turns a blind eye to their limitations and dangers Apart from many technical difficulties, patients with severe and even moderately advanced cirrhosis are still beyond surgical help and the emergency treatment of ruptured varices remains controversial and, on the whole, unsatisfactory (George Crile contributes a useful chapter on transœsophageal ligation of varices) Mr Hunt deals with technical matters and alternative operations in a series of appendices from which no detail of practical importance has been omitted, and a series of succinct case-histories complete the work The illustrations are a credit to the writer's technical and clinical team and to his publishers

New Developments in Analytical Psychology (London Routledge & Kegan Paul 1957 Pp 214 25*s*)—This book by Dr Michael Fordham contains nine essays on various topics of analytical psychology The first four, which are the longest, are concerned with biological theory and the concept of archetypes, the archetypes and synchronicity, image and symbol, and the transference As in most Jungian writings, a difficult subject is not simplified for the uninitiated by conciseness or by definition of the ideas considered, but most psychotherapists should glean occasional kernels The last five chapters are concerned with theories of child development, the analysis of the child, and the child-guidance approach to marriage, and are less theoretical in presentation

Hospital Coccal Infections (Association of Clinical Pathologists 1958 Pp 39 3*s* 6*d*)—Last year a symposium on hospital coccal infections was organised by the Association of Clinical Pathologists and the Medical Research Council Committee on Cross-infection in Hospital, and we gave some account of it [1] The papers by the principal speakers have now been published, together with summaries of the discussions, in a booklet, which may be obtained from the Swan Press, Ltd, 20, Bakers Row, Farringdon Road, London, E C 1 The editors are Dr R E O Williams and Dr R A Shooter

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[1] See *Lancet*, 1957, i, 92

New Inventions

THE ST THOMAS'S HOSPITAL NERVE STIMULATOR

IN THE DIAGNOSIS OF PROLONGED APNŒA

UNEXPECTEDLY prolonged response to muscle relaxants has been reported increasingly often in recent years [1–4], and its possible theoretical causes have been outlined [5] One of the principal difficulties facing most anæsthetists is to determine whether the failure of return of full muscle power is due to a central cause affecting the brain (e g, analgesic, anæsthetic, or excess of carbon dioxide), or to peripheral weakness caused by prolongation of the neuromuscular block No ordinary clinical examination can differentiate between these two causes, but electrical stimulation of a peripheral nerve (e g, ulnar) will immediately reveal whether the skeletal musculature is responding to impulses or not, provided the intensity of the stimulus (i e, the current) is sufficient

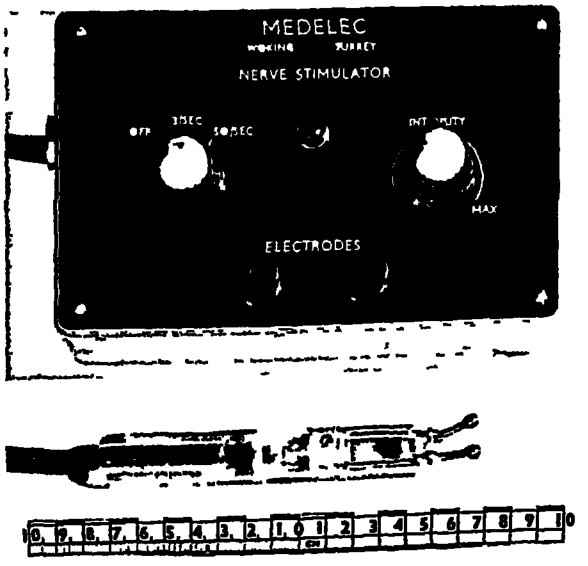

Fig 1.

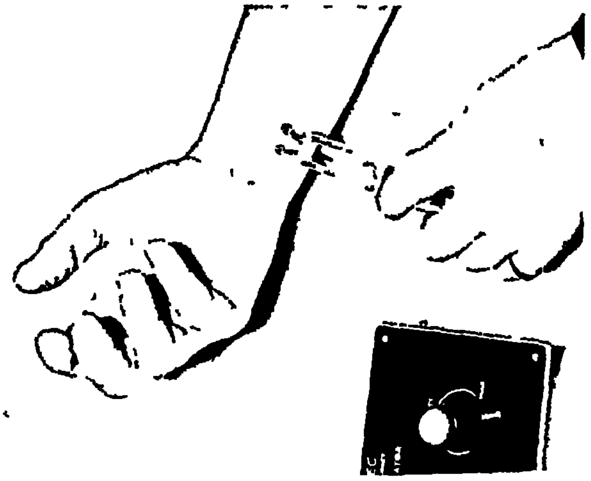

Fig 2

In the past, electrical stimulators have not been readily available, but during the last five years various models have been in use at this hospital for research purposes The present apparatus (fig 1) has been designed for use in the operating theatre and is now produced commercially It is capable of stimulating at either slow rates (twitch—3 per sec) or fast rates (tetanus—50 per sec) In man, ordinary volition uses a rate varying from 30 to 50 per sec according to the force of the muscle contraction The intensity of the stimulus can be altered at will, but in the unconscious subject it is advisable to use the maximum possible to ensure that all the muscle-fibres served by that nerve will contract

In the event of an abnormal response to a muscle relaxant this machine can be used to stimulate the ulnar nerve at the wrist or the elbow (fig 2) Then, if neuromuscular block is present, the 4th and 5th fingers will not move, on the other hand, if normal neuromuscular transmission is present, the typical picture of main-en-griffe will result

We believe this nerve-stimulator will prove very useful to anæsthetists It can be used to study the action of muscle relaxants during routine anæsthesia or (by changing the electrodes) to detect the whereabouts of the facial nerve at operation

Our thanks are due to Dr P Bauwens for his helpful advice

The St Thomas's Hospital Nerve Stimulator can be obtained from Medelec Limited, Woking, Surrey

T H CHRISTIE
M B Lond, F F A R C S
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St Thomas's Hospital,
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1 Hunter, A R *Brit med J* 1956, ii, 919
2 Foster, P A *Brit J Anæsth* 1956, 28, 488
3 Bourne, J G, Shackleton, P *Brit med J* 1956, ii, 1485
4 Burchell, G B *Brit J Anæsth* 1957, 29, 127
5 Churchill-Davidson, H C *Anesthesiology*, 1956, 17, 88, *Brit med Bull* 1958, 14, 31

THE LANCET

LONDON 12 APRIL 1958

Iodine Prophylaxis of Goitre

"ENDEMIC goitre is the easiest known disease to prevent," said MARINE[1] in 1915 This confident remark has been fully justified by subsequent experience The United States, Switzerland, and New Zealand have been using prophylactic iodine for several decades, and goitre has notably declined in all three countries[2] Similar measures have been introduced more recently in Canada, Mexico, Guatemala, Colombia, Peru, Argentina, Paraguay, Sweden, Holland, Poland, Rumania, Yugoslavia, Hungary, Czechoslovakia, Italy, and parts of Australia[2] These measures have been applied with varying degrees of thoroughness, and in most cases too recently for proper assessment of the results Nevertheless it is impressive that so many countries should think it worth taking official action to increase the iodine intake of their inhabitants So far this country has made no attempt to eliminate goitre The iodisation of salt was recommended by a subcommittee of the Medical Research Council in 1944[3], and this recommendation was widely supported[4] In 1950 the Government of the day seemed about to take action,[5] but in the event nothing was done So many other countries are now ahead of us in this simple public-health measure that official inertia is making us look somewhat oldfashioned

We do not know what induced the Government to withdraw its proposed measures for iodising salt, but there seem to be at least three rational grounds for hesitation

One is the possibility that in this country other goitrogenic factors outweigh the effects of iodine deficiency In clinical practice occasional goitres are certainly not due to iodine deficiency—for example, those due to chronic thyroiditis, the goitrogenic drugs, and hereditary causes All these are rare, however, and they are distinguished from ordinary sporadic goitre by their tendency to be associated with hypothyroidism Our diet is unlikely to include significant amounts of goitrogenic substances unless we consistently eat raw turnips[6] or drink milk from cows fed on related cruciferous plants[7], and if such substances were an important constituent of the diet we should expect to encounter hypothyroidism as well as goitre ASTWOOD[6] has pointed out that the thyroid is likely to compensate better for iodine deficiency than for a chemically induced block in thyroxine synthesis The fact that the ordinary goitre is practically never associated with hypothyroidism is indirect evidence that it is caused by iodine deficiency rather than by a positive goitrogen More direct evidence has been provided by BURRELL and FRASER,[8] who have shown that some non-toxic goitres studied in London were unduly avid for radio-iodine but that this avidity could be abolished by brief treatment with small doses of iodide While there is no proof that iodine deficiency is the main factor in the causation of goitre in this country, there is at least no evidence incompatible with that hypothesis

A second possible reason for official hesitation is the argument that goitre in this country is not of sufficient practical importance to warrant action on a national scale In most cases, it may be reasoned, the inconvenience of having a goitre is cosmetic rather than medical Admittedly it has never been proved that the common accompaniments of endemic goitre—cretinism and deaf-mutism—are themselves caused by iodine deficiency, and it is still open to question whether a reduction in the incidence of simple goitre would be associated with a similar diminution in the incidence of toxic goitre and thyroid cancer Yet even in the absence of these complications there are disadvantages about having nodules in one's thyroid In his article at the beginning of this week's issue Mr SELWYN TAYLOR traces the origin of thyroid nodules back to a stage of simple hyperplasia, and it is at this stage (probably about the age of puberty) that we believe goitre to be preventable Once puberty goitre has developed, thyroxine or thyroid extract is a rational, and often an effective, treatment But when nodules are present the surgeon's knife is the only useful therapeutic weapon This is an expensive weapon, involving the cost of perhaps two weeks' stay in hospital as well as that of the operation We have no way of estimating how often this operation is being performed, but the Registrar-General's review of hospital inpatients for 1951 shows that patients with non-toxic goitre comprised nearly 1% of the female non-obstetric admissions to teaching hospitals If most of these admissions could be avoided the reduction in hospital costs, though not spectacular, should at least offset the cost of iodising salt On balance iodine prophylaxis could be expected to pay for itself, and even yield a modest profit to the community

The third, and perhaps most cogent, reason for doubt about the desirability of iodine prophylaxis is disinclination to compel people to eat what experts think is good for them This attitude is by no means wholly irrational, since the conclusions of Science are never final but are merely the best current approximations to truth During the war the fortification of margarine and other foodstuffs with vitamin D appeared, in the light of contemporary knowledge, to be wholly beneficent, but we now know that the addition of this vitamin can easily be overdone and may be a factor in the causation of infantile hypercalcæmia[9] At present the addition of small quantities of iodine to salt seems to be entirely unobjectionable and unlikely to do anyone the slightest harm, but no-one can unreservedly guarantee that this will turn out to be true A deeper, if less rational, objection along the same lines is that further encroachment on the liberty of individuals should be resisted The nature of our complex civilisation demands that we submit to many restrictions on our freedom of action as individuals, but our aim should be to keep these restrictions to the bare minimum necessary for the smooth running of society Hence it seems desirable that, although iodine prophylaxis should be introduced as soon and on as wide a scale as possible, some loophole should be left by which those who wish can avoid receiving iodine From this point of view an excellent vehicle for the distribution of iodine would be salt, as was recommended by the M R C subcommittee, and much technical information has been accumulated about methods of iodising this material [10] What is required is that some 95% of all salt used domestically shall be iodised at the level recommended by the M R C Anyone ordering salt would automatically be given iodised salt unless he specifically asked for non-iodised In this way the majority could be protected against goitre without encroaching on personal liberty TAYLOR reaches a similar conclusion The time has surely come for further thought by the Government

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[1] See Kimball, O P *Bull World Hlth Org* 1953, 9, 241

[2] Kelly F C, Snedden, W W *ibid* 1958, 18 5

[3] Goitre Subcommittee Medical Research Council *Lancet*, 1944 i 107

[4] *Lancet* 1944 i, 121 *ibid* 1955, ii, 125 Report of the Committee on Nutrition British Medical Association, London, 1950 *Brit med J* 1950, i, 654 *Times*, March 23, 1950

[5] *Lancet*, 1950 i 632

[6] Astwood, E B *Ann intern Med* 1949, 30 1087

[7] Clements, F W, Wishart, J W *Metabolism*, 1956, 5, 623

[8] Burrell, C D Fraser R *Quart J Med* 1957, 26, 559

[9] See *Lancet*, 1956, i, 1052

Bleeding Varices

THE treatment of ruptured œsophageal varices may have to be undertaken by comparatively inexperienced surgeons at short notice and under difficult circumstances The coming of blood-banks inspired the first attempts to deal actively with this emergency The dramatic effect of prompt massive transfusion on most forms of acute hæmorrhage encouraged the hope that this would prove the life-saving first-aid treatment of bleeding cirrhotics Such hope was soon dispelled experience showed that transfusion alone did not reduce mortality, and that in at least three different ways it could be a contributory cause of death It first became apparent that dilution of the circulating clotting factors by transfused blood made cirrhotic patients, with their already depleted stores, the least suitable subjects on whom to test an excessive faith in banked blood It was then recognised that hepatic failure, precipitated by large nitrogenous blood-meals, was as potent a cause of death as circulatory collapse from blood-loss itself, and that the greater the amount of blood given, the greater the amount the patient could shed into his gastrointestinal tract Most recently attention has turned to citric-acid intoxication [11]—a real danger when liver function is impaired Blood-transfusion remains an invaluable supportive measure, but complete reliance cannot be placed on it

If the phase of massive transfusions was one of unfulfilled hope, BLAKEMORE hardly exaggerates when he describes the next phase as the "carnage of cirrhotics" [12] It coincided with a tremendous advance in the management of bleeding peptic ulcers—the wider recognition that seemingly moribund patients could be restored to health by judiciously timed operations and by expert perioperative management But the knife, which brought new hope to many ulcer patients, spelt doom to the majority of bleeding cirrhotics they too were operated on for bleeding ulcers, and they died of hepatic failure This era left the bleeding-ulcer majority deeply indebted to the hapless minority of bleeding cirrhotics, it ended not with dramatic advances in surgical technique but with the growing realisation that cirrhotics can ill withstand even the best of surgery In at least 70% of hæmatemeses a bleeding ulcer can be diagnosed with fair certainty, but if bleeding cirrhotics are to be given a fair deal, the remaining 30% should be treated (until a diagnosis is clearly established) as potential cases of ruptured varices This demands an entirely different therapeutic approach In the potential cirrhotic the primary aim is not to replace but to stop the blood-loss, and laparotomy is not a valid diagnostic procedure

Differential balloon-tamponade, which serves the dual purpose of diagnosis and treatment,[12-14] has been a real advance in the management of these cases

It is carried out with a specially designed three-lumened tube, equipped with a sausage-shaped œsophageal balloon and a spherical gastric balloon After accurate positioning of the œsophageal balloon by preliminary gastric inflation, air is slowly introduced into the naso-œsophageal tube The distending balloon in the œsophagus encompasses the varices above the cardia, and when the pressure inside it (measured by a built-in mercury manometer) rises above the patient's portal pressure, bleeding ceases BLAKEMORE [12] rightly insists that the balloon used should be specially designed and tested for this purpose

If inflation of the œsophageal balloon does not arrest the bleeding—and this can be verified by aspirating through the nasogastric tube—the gastric balloon must be inflated As much as 400 c cm of air may have to be introduced into this stouter bag, and an upward pull of 2 lb is usually needed to compress effectively the stomach against the diaphragm

If such traction-tamponade does not control the bleeding, it is reasonable to assume that the bleeding-point lies distal to the proximal half of the stomach—probably in an ulcer crater—and some surgeons would attempt to localise it by injecting small amounts of barium into the feeding tube If the bleeding is arrested, a ruptured varix in the upper stomach is the likeliest diagnosis Unfortunately such a finding commits the surgeon to almost immediate operation Not only is compression of the proximal stomach for more than a few hours intolerable to the patient it also leads to rapid deterioration of the gastric mucosa, and, often within twenty-four hours, to ulceration and gangrene It is true that only about 10% of ruptured varices are on the gastric side of the cardia It is also true that the outlook for these patients is poor from the start, and that many have to be operated on as a last desperate measure Traction-tamponade itself, however, makes laparotomy imperative, whereas conservative measures alone—skilled sedation, carefully regulated drip-transfusion, and prophylaxis of liver failure—occasionally tide patients over the acute episode and allow the surgeon to intervene at a more opportune moment

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[10] Holman J C M *Bull World Hlth Org* 1958, 18, 255

[11] See *Lancet*, 1957, ii, 1152

[12] Blakemore, A H *in* Current Surgical Management (edited by J H Mulholland, E H Ellison, and S E Friesen) Philadelphia, 1957

[13] Sengstaken, R W, Blakemore, A H *Ann Surg* 1950, 131, 781

[14] Boerema, I *Congr int Gastroent* Paris, 1954 See also *Lancet*, March 29, 1958, p 681

In contrast to traction-tamponade of the stomach, œsophageal tamponade can be maintained for three or four days if necessary Continued distension of the lower gullet is very unpleasant, but it is rarely intolerable, and nasal ulceration and necrosis can usually be prevented by nursing care and antibiotics There is rarely justification for rushing unprepared into operation on the ground that œsophageal tamponade can be maintained no longer Unfortunately, often what is loosely described (and justly decried) as "œsophageal" tamponade is, in fact, half-hearted traction-tamponade on the stomach It is easy to control bleeding from a ruptured œsophageal varix by compressing its feeding vessel in the upper stomach—and when some improvised contraption is used this is what usually happens—but such a manœuvre is both unnecessary and unpleasant When the varices are in the œsophagus, œsophageal balloon-tamponade properly performed will always provide at least a breathing-space for improving the patient's general condition and summoning expert surgical help

Linton and Ellis [15] have found that it is best to prepare patients for operation as soon as the hæmorrhage is controlled These workers reported 20 cases in which they had performed transthoracic transœsophageal ligation of the bleeding varices either with a view to later shunt operation or as a definitive measure 2 patients died as a direct outcome of the operation, and 3 succumbed to liver failure or recurrent bleeding before a shunt procedure could be done, but in the remaining 15 it was possible to construct, after varying intervals, a portocaval or a lienorenal shunt Transœsophageal ligation of the bleeding varices has the supreme merits of comparative safety and simplicity [16-18], but usually it is of no more than temporary benefit. Crile [19] has achieved some good long-term results in patients with extrahepatic blocks [19], but Linton [20] found that in more than a third of cirrhotics the bleeding recurred in a few weeks or months In this country Tanner [21] devised an operation in which the mid-stomach was transected and resutured after division of all the vasa brevia and of all the branches of the left gastric vein which drained the proximal half Unfortunately, several patients had recurrent bleeds, and, though postmortem injection studies showed no appreciable flow across the gastric suture-line, anastomotic branches between the œsophageal and phrenic veins had apparently maintained a dangerously high pressure in the varices This led Tanner to devise a subcardiac porto-azygos disconnection [22] By an abdominothoracic approach he frees the lowest five centimetres of the œsophagus and the uppermost five centimetres of the lesser and greater curves of the stomach from all external vascular connections, the stomach is then completely transected and resutured five centimetres below the cardia, leaving just enough blood-supply from the œsophagus to nourish the small upper gastric segment Tanner [23] reported that in each of 11 cases of acutely bleeding œsophageal varices this operation arrested the bleeding, but some months later 2 patients bled again, and a further patient succumbed to hæmorrhage from gastric ulceration at the suture-line He also performed the operation in many cases as an interval procedure, with excellent long-term effects This is very encouraging, but post-vagotomy stasis is an almost inevitable sequel to the operation, and, though a few days' gastric suction are an adequate countermeasure in most cases, a second-stage pyloroplasty had to be performed in 2 of Tanner's patients Hunt [18] points out that the operation can be extremely difficult, and he suggests that it is less likely to succeed in cases of cirrhosis than in cases of extrahepatic obstruction

Of the other possible operations, more or less extensive gastric and gastroœsophageal resections, pioneered in America by Phemister and Humphries,[24] may gain a place in the emergency as well as in the interval treatment of ruptured varices [25, 26] Hepatic-artery ligation,[27] though it cannot be recommended in its present form,[28] may yet emerge from obscurity disguised as "portalisation of the artery" [29] Splenectomy still has a few indications [18] and a few able if cautious advocates [30] Shunt procedures,[31-38] now widely regarded as the surgical treatment of choice, have already been performed for acute hæmorrhage O'Sullivan and Payne [39] reported 9 cases submitted to this operation as emergencies 3 died in the immediate postoperative phase, and 3 died later from liver failure, but none of the 6 who survived operation bled again "Arterialisation" of the liver may further widen the scope of shunt operations [18, 40-43] The threat of hepatic failure is at present the most stringent limiting factor in the selection of patients for operation; and, even though few patients with advanced cirrhosis are selected, it remains by far the commonest cause of postoperative death "Hepatic arterialisation' aims at preventing this complication Theoretically it can be achieved by connecting the hepatic end of the divided portal vein to the proximal end of a divided and dispensable artery of the region But no such procedure has yet graduated from the experimental class—and even at that level results are not wholly encouraging [44] Nevertheless further progress may be along these lines

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[15] Linton, R R., Ellis, D S *J Amer med Ass* 1956, 160, 1017
[16] Boerema, I *Arch chir Ned* 1949, 1, 253
[17] Crile G, Jr *Surg Gynec Obstet* 1953 96 573
[18] Hunt A. H Portal Hypertension. Edinburgh 1958
[19] Crile G Jr *in* Current Surgical Management Philadelphia, 1957
[20] Linton, R. R. *Gastroenterology*, 1953 24 1
[21] Tanner, N C. *Proc R. Soc Med* 1950 43, 147
[22] Tanner, N C. *ibid* 1954, 47, 475
[23] Tanner, N C *Ann R Coll Surg Engl* 1958, 22, 30
[24] Phemister D B, Humphreys, E. M. *Ann Surg* 1947, 126, 397
[25] Wangensteen, O H *Surgery* 1956, 39, 1
[26] Allen, J G *in* Current Surgical Management Philadelphia, 1957
[27] Rienhoff, W J Jr *Bull Johns Hopk Hosp* 1951, 88, 368
[28] Altmeier, W A *Arch Surg, Chicago*, 1955, 71, 571
[29] Leger, L, Albot G, Vaille L. *Pr méd* 1955, 63, 1290
[30] Moore, R M Singleton, A O *in* Current Surgical Management. Philadelphia 1957
[31] Blakemore, A H, Lord J W *Ann Surg* 1945, 122, 476
[32] Linton, R R *ibid* 1949 134, 433
[33] Ellis, D S, Linton, R R., Jones, C M *New Engl J Med* 1956, 254, 931
[34] Welch C. S *ibid* 1949, 134, 433
[35] Learmonth, J R. *Ann R Coll Surg Engl* 1947, 1, 299
[36] Walker, R. M *Lancet* 1957 i, 57
[37] Ravdin, I S *Ann R Coll Surg Engl* 1957, 20, 71
[38] *Lancet* 1957 ii 29
[39] O Sullivan W D, Payne, M A. *Surg Gynec Obstet* 1956, 102, 668
[40] Hunt, A H. *Brit med J* 1952, ii 4
[41] Cohn, R., Herrod, C. *Surgery*, 1952, 32, 214
[42] Fisher, B Russ, C, Updegraff, H., Fisher, E *Arch Surg, Chicago*, 1954 69 263
[43] Fisher, B, Russ C., Fedor, E., Wilde, R., Engstrom, P, Fisher, E. *Surgery* 1955, 38 181
[44] McCredie J A, Doggart, J R., Welbourn, R. B *Brit J Surg* 1957, 45 83

Pituitary Tumours

Of the many pituitary tumours most are adenomas, and some are Rathke pouch tumours—otherwise called craniopharyngiomas, indicating their origin in fragments of the embryonic evagination of the roof of the mouth which becomes the adenohypophysis. Primary malignant lesions are rare. The adenomas usually present in adult life, radiographs show much ballooning of the sella turcica and erosion of the clinoid processes. The Rathke pouch tumours often give symptoms in childhood, they are extrasellar more often than intrasellar, with a typical radiographic picture of calcification above a much less expanded pituitary fossa. Any pituitary tumour may threaten life and vision by pressing on nervous tissue or by causing internal hydrocephalus. Symptoms include headache, nausea, vomiting, blurred vision (sometimes transient or uniocular), and bitemporal or other scotomas, less common are epilepsy, trigeminal pain (not always due to malignant lesions), hemiparesis, diplopia, ophthalmoplegia, and papillœdema. Involvement of the hypothalamus may give rise to obesity, thirst, polyuria, thermal disturbances, and somnolence.

Such dramatic and urgent events may obscure the fact that pituitary tumours usually have an endocrine as well as a neurological aspect, and that the endocrine effects often long precede the neurological. Jefferson[1] studied 131 cases of chromophobe adenoma and 57 cases of Rathke pouch tumour. In half the male patients with chromophobe adenoma there was a history of sparseness of facial hair, sometimes with definite lack of body hair, usually starting in the late 'teens or early twenties, and preceding visual symptoms by as much as 45 years. The first symptom in half the female patients was upset in the menstrual rhythm, followed after a shorter interval ($5^1/_2$ years on average) by visual symptoms. It has long been accepted that chromophobe adenomas (in contrast to the hypersecreting eosinophilic adenomas, which give increased somatic growth, and the very rare basophilic adenomas) do not contain active hormones but tend to cause hypopituitarism by crowding out the other cellular elements of the hypophysis. But might not the chromophobe adenoma be regarded as a group of cells which multiply in an effort to compensate for some metabolic abnormality?[1] Russfield and her colleagues[2] think so. They believe that the primary defect may be atrophy and insufficiency of the gonads or thyroid, that this eventually stimulates the pituitary to hyperplasia and neoplasia, that some "chromophobe adenomas" do secrete hormones which can cause hyperplasia of the adrenal glands and other "target organs", indeed that the difference between the tumours of acromegalic and non-acromegalic patients is often quantitative rather than qualitative. Be that as it may, it is beyond question that the various types of pituitary tumour can destroy the pituitary, and so lead to atrophy of the adrenals, thyroid, gonads, and genital tract, and to the clinical syndrome of severe hypopituitarism.[3] It seems likely, too, that pituitary insufficiency from pituitary tumours is incomplete more often than complete, and the incomplete form can be a more elusive diagnostic problem. At the Mayo Clinic Troen and Rynearson[4] found evidence of 41 mild and 25 severe cases of hypopituitarism in 153 patients before operation. Endocrine insufficiency is an important source of ill health in such cases and demands treatment with, say, cortisone, testosterone, or thyroid, or combinations of these, according to the needs disclosed by clinical and laboratory assessment. Conversely, the finding of an endocrine disorder may demand a radiograph of the skull, since there may be no other clinical pointer to a pituitary tumour.

Patients with untreated hypopituitarism are liable to attacks of mental confusion or coma, often associated with bizarre neurological signs. The attacks may be precipitated by intracranial operations, hæmorrhage into a pituitary tumour, infections, drugs, or anæsthesia, and be associated with hypoglycæmia, or sodium depletion, or water retention, or cerebral anoxia.[5] Severe endocrine failure, especially of the adrenal cortex, seems to be the most important common factor in these catastrophes, and in the presence of a big pituitary tumour there is real danger that such attacks be wrongly attributed to, say, internal hydrocephalus or pressure on vital cerebral structures, and so lives may be lost for want of cortisone therapy. Jefferson,[6] in a retrospective study covering periods before the introduction of modern endocrine treatment, considered that of 61 deaths in cases of pituitary tumour 26 were due wholly or partly to endocrine failure. After operations on the pituitary, complications are commoner in patients with hypopituitarism, and their incidence is reduced in these patients by giving cortisone before operation.[4] Although many postoperative complications and deaths are not readily explained by endocrine disorder,[4 5] cortisone reduces the general mortality from operations on pituitary tumours, irrespective of the preoperative and postoperative endocrine status.[4]

In the treatment of the tumour mass, operation is rarely required in the absence of visual disturbance, but it is imperative if there are urgent pressure symptoms. With Rathke pouch tumours, deep X-ray therapy is unsatisfactory and operation risky. There is less certainty about the management of pituitary adenomas with mild to moderate visual loss. At the Lahey Clinic[7] in 1932–49, 89 patients were treated for visual loss by irradiation only, but of this number 56 were operated on subsequently because vision was not held at a useful level, indeed, the vision of some was so greatly reduced that they were not benefited by surgical removal of their adenomas. Since 1950 a method has been used whereby a tumour dose of 4000r can be delivered with safety. Of 66 patients with visual loss so treated in

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[1] Jefferson, A A *Ann R Coll Surg Engl* 1957, 21, 358

[2] Russfield A B, Reiner, L, Klaus, H *Amer J Path* 1956, 32, 1055

[3] Sheehan H L, Summers V K *Quart J Med* 1949, 18 319

[4] Troen, P, Rynearson, E H *J clin Endocrin* 1956, 16, 747

[5] Caughey, J L, Garrod, O *Brit med J* 1954, i, 554

[6] Jefferson A A *J Neurol Neurosurg Psychiat* 1957, 20, 265

[7] Horrax, G *Arch Neurol Psychiat* 1958, 79, 1

1950–55, only 8 have required operation. These preliminary results are encouraging, but during therapy there is need for the most careful evaluation of visual tests, for which the neurosurgeon should be responsible[8] Patients with pituitary adenomas who are correctly treated can survive a long time[1] These cases are well worth the thoughtful care which must be given to their diagnosis and management.

Annotations

THE EVOLUTION OF VISION

WHEN Lister returned from Scotland, surgical London flocked to his first lecture to hear the latest news of his technique, but he had been interested in the curdling of milk, and told the audience, instead, about the *Bacillus lactis* that he had discovered Introducing his Lister oration on March 28 with this story, Sir Stewart Duke-Elder elected to talk, not of any detail of eye surgery, but of the Emergence of Vision in the Animal World He pointed out that whereas most lower animals depend largely on other senses, and their brains (" nose-brains ") are largely devoted to smell, the human brain is an " eye-brain ", with its receptive area behind, large association areas, and centres for control and coordination further forward

Sensitivity to light is first manifest as a motor reaction An amœba will move away from light as it will from any other noxious stimulus, some insects move not directly towards or away from a light but in a direction at a constant angle to it By this means an ant, moving at a constant angle to the sun's rays, can find its way back to its home, but if it is imprisoned in the dark while the sun moves through an arc, when released it will set off in the wrong direction Moreover, if the source of light is, unlike the sun, near by, moving at a constant angle will involve moving in a spiral, that is why the moth flies to its death in a candle flame Bees can orient themselves by the sun, but can make a correction for the time of day, and so can birds Manx shearwater released in America flew, lost, in any direction on an overcast day, on a sunny day they oriented themselves correctly in 40 seconds, and flew across the Atlantic, each to its own particular burrow off the west coast of England

These reactions are unlikely to involve visual *perceptions* Plants too can react to light—*Hedysarum girans* nods to a passing cloud—and machines can follow a torch In animals purposeful appreciation can reverse the automatism of a response thus a cockroach, which normally avoids light, can be taught to approach it if there is a dark shelter underneath The first animal to show such intelligent appreciation is the earthworm, which has many light-sensitive cells, and normally approaches a dim light and avoids a bright one, but it can be conditioned to respond in other ways Thus vision for the first time is associated with awareness the animal can see, though it cannot form an image of anything Appreciation of movement in the outside world is evident in the molluscs any movement causes the protrusion of the organs of chemical and tactile sense But sensitivity to movement is important in an animal as high as the rabbit, which will run into a stationary man Form vision appears in cephalopods—an octopus can distinguish between vertical and horizontal lines—and colour vision in certain insects, though it is important only in fishes, birds, and primates

Development of vision depends on environment In deep-sea fishes, which live in darkness, it is lost, in small mammals, such as the dog and cat, living near the ground, it is less important than tactile and olfactory sensation The highest development has come in certain fishes (living in a three-dimensional world) and more particularly in birds and arboreal creatures—tree-snakes, tree-shrews, and primates The swaying habitat of branches necessitated the development of prehensile limbs and fine stereoscopic vision, moreover, "the security of the tree-tops allowed an escape from the urgent fears of life on the ground with its teeming population of predators, so that the senses, not constantly alert for danger, turned to other things" New explorations by hand and eye gave rise to new associations, curiosity, and inventiveness—the foundation for the intellectual supremacy of man

A chimpanzee, unlike lower mammals, will amuse himself visually—by looking at the world upside down or through a hole, or even with a kaleidoscope This is the first indication, says Sir Stewart, " that vision has become elevated from the level of biological usefulness to approach that of æstheticism " In evolution, he says, there are stages when something new appears different from its constituent parts, thus the molecule differs from its atoms, and other stages are marked by the emergence of life and of consciousness In the evolution of vision the first stage is that of the motor reaction, the second that of perceptual vision, which emerges in the earthworm with a brain-ganglion, for it needs central nervous organisation The third emergent is imaginative vision, exploratory and creative, dependent on the development of forebrain and association areas

We know that animals see, but not what they see Analysis of our own perceptions is hard, analysis of those of dumb creatures is impossible Sensations can be appreciated and interpreted only through our perceptions, we know of no corresponding higher stage for the interpretation of our perceptions But the brain of a bee, which can correct for changes in the sun's position with time, is only $^{1}/_{10}$ in across, the brain of man is vastly bigger, and may expand further New capacities and understandings may well emerge—given time, for the apes threw sticks and stones, and we throw atom bombs

NOMENCLATURE OF PATHOGENIC FUNGI

THE former unsatisfactory state of the nomenclature of fungi pathogenic to man was due, in some measure, to inadequate description of newly named species, which led to the same species being renamed from time to time by different authors, also to the tendency to variation inherent in many fungi, the unidentified variant often being accorded specific rank These faults gave rise to multiplication of names, and in a work on pathogenic fungi published twenty years ago some 746 " species " were recorded Since then a new and more scientific interest in fungus diseases, particularly the systemic infections, has been aroused by the discovery of their widespread distribution in some countries, mainly through mass radiography of the chest and routine testing for specific cutaneous sensitivity to fungus antigens

Through the work of the Committee on Medical and Veterinary Mycopathology of the International Association of Microbiologists, international agreement on the

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8 Ray B S *ibid* p 5

use of recommended names has been secured to a great extent, and revised nomenclature is in general use in the countries of North and South America and the British Commonwealth, and to a lesser degree in some European countries. To ensure uniformity and avoid confusion, authors of papers on fungus diseases and medical mycology should consult the revised authoritative list of names of pathogenic fungi and fungus diseases.[1]

THE UNHEALTHY AREAS

EVER since Farr, the General Register Office has been disturbed by the striking disparities in death-rates between different areas in England and Wales. Such disparities are important for two reasons: first, as a spur to local public-health action, and secondly as suggestive clues in epidemiological studies of disease causation. In this respect, the analysis of mortality by geography supplements its dissection by occupation, and by the publication of the volume on area mortality,[2] the Registrar General completes the major studies based on the national experience during the years around the 1951 Census.

The geographical distribution of mortality in England and Wales follows a set pattern with higher death-rates in the north and west. In the north-west region both male and female mortality-rates were at least 10% above the national average, and an excessive infant mortality there completes the evidence of an adverse social environment. As the Registrar General remarks, climate in itself is unlikely to be of major importance. Indeed a detailed survey of the death-rates by cause in different areas strongly suggests the relevance of atmospheric pollution. Bronchitis, for example, bears much more heavily on both sides in the north-western region, and there is a marked gradient in mortality from the standardised mortality ratios for both sexes. Male mortality, for example, rises from 62% of the national average in the rural districts to 139% in the provincial conurbations. Greater London, with a rate of 123 for male and 117 for females, is still seriously afflicted, particularly in districts such as Shoreditch and Southwark where the smoke pall lies heavy.

Some of the social and selective factors which determine the incidence of disease and death are apparent in the experience of the county boroughs largely devoted to major industries where either men or men and women may be employed. In cotton towns such as Oldham, the death-rate among women is 23% above the national average. Some of this excess can be explained by death-rates from bronchitis more than twice the rate for women in the country as a whole, and it is possible that the effects of employment outside the home are superimposed on the results of a smoky and crowded domestic environment. It is perhaps significant that in towns such as Oldham and Rochdale the infant-mortality rate is among the highest in the country.

The men of the mining areas of South Wales have the high mortality from respiratory diseases usually associated with this occupation, but the women of the same areas shared this excess of mortality. In Merthyr Tydfil, for example, the death-rate among females was 23% above the national average. These findings emphasise how death-rates by occupation must be looked at against the perspective of the mortality patterns of the areas where major industry is sited. The interpretation of death-rates whether by occupation or area also depends on the community history of the ebb and flow of migration in step with the expansion and contraction of the basic industry on which depends the inhabitants' standard of life. The draining of the fittest and most vigorous men away from derelict areas, agricultural or industrial, has always been a melancholy spectacle, and its end-results are evident in the vital statistics of the residual population. Whether because of similar migration of the fit single women, or through some process of assortive mating by emigrant males, similar trends are evident in the mortality of the women in these areas.

Any realistic assessment of this latest publication by the General Register Office will thus require the most careful partitioning of blame for excessive mortality between occupational, environmental, and socio-economic factors. There is, however, in these tables of assembled facts no reason for complacency about the health of many of our most important areas and much to stimulate thought, research, and action.

CLOSTRIDIUM WELCHII FOOD-POISONING FROM COLD CHICKEN

COLD chicken is a traditional item in the diet of the convalescent, and indeed of any patient whose digestion is considered unequal to the rigours of ordinary diet. For its preparation a big hospital may have to boil some twenty or more fowls at a time. These are usually cooked in a large boiler in water for some two to three hours, after which they are removed from the boiler and allowed to cool at room temperature before being refrigerated. This process is not without risks of bacterial contamination, which may lead to food-poisoning. In the United States McClung[1] reported outbreaks, among the customers of a large public cafeteria, of *Clostridium welchii* food-poisoning conveyed by chicken cooked one day and served the next. On page 787 of this issue, Dr McNicol and Miss McKillop show that this kind of food-poisoning may also strike hospital patients. As they say, the victims are usually those given light diet. Many of these may suffer severely, and some, especially among those recovering from major abdominal operations, may die from the infection, which does not usually cause a very serious illness in a healthy adult.

In hospitals generally, some of the unexplained outbreaks termed "hospital diarrhœa" might be proved to be due to *Cl. welchii* conveyed by cold chicken if only the appropriate investigations were made. There is nothing technically difficult about isolating and identifying *Cl. welchii*, the hard thing is to persuade doctors and nurses that they should demand a proper investigation of all cases of diarrhœa in hospital. Diarrhœa that is relatively mild and brief is often ignored, or the patient is assured that he has probably had a little too much aperient. Where any bacteriological examination of an outbreak is undertaken, usually only one or two samples of stool are submitted from the few patients whose diarrhœa persists rather longer than that of the others. Salmonellas and shigellas are not found, *Cl. welchii*, even if it is found, is perhaps dismissed as of doubtful significance because most humans carry it in the intestine, and so yet another incident is unhelpfully diagnosed as "hospital diarrhœa." In the investigation of cases of diarrhœa in a hospital ward there is need (as in McNicol and McKillop's experience) for a full history and a diligent search for an article of food common to all who have had even minor symptoms Cold chicken is so acceptable a delicacy that it is seldom that any is left over to be examined, instead, the remainder will probably have been shared among some for whom it was not primarily intended Examination of these also, whether they have symptoms or not, is a necessary and often very helpful part of the investigation For physical as well as other reasons, however, it often proves difficult to secure for laboratory examination samples of stool from all at risk

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[1] Nomenclature of Fungi Pathogenic to Man and Animals: names recommended for use in Great Britain. Medical Research Council memorandum no. 23 (revised edition, 1958). H.M. Stationery Office. Pp. 15. 1s. 3d.

[2] The Registrar General's Decennial Supplement, England and Wales, 1951. Area Mortality. London: H.M. Stationery Office. Pp. 82. £3 10s.

[1] McClung, L. S. *J. Bact.* 1945, 50, 229.

Chiefs of wards do not always realise that, for many reasons, the reporting and investigation of hospital diarrhœa by their staffs is commonly less than adequate McNicol and McKillop emphasise that they have gained something from the use of rectal swabs to collect the samples they needed Some evidence reported by Hobbs et al[2] suggests that examination of rectal swabs for *Cl welchii* may be less certain of giving a positive result than examination of a sample of stool Against this, however, use of the rectal swab makes it possible to ensure that a sample is secured for examination from all at risk, and the finding of many *Cl welchii* in the fæces of an abnormally high proportion of those at risk often constitutes the first real evidence that this form of food-poisoning is the cause of an outbreak of diarrhœa

In such outbreaks the *Cl welchii* isolated from the intestines of the patients is often in heat-resistant form (withstanding 100°C for an hour or more) and is often non-hæmolytic on horse-blood agar Sometimes typing of such strains by agglutinating antisera reinforces the probability of a common source of infection,[2-4] but many strains are still untypable Moreover it is untrue that *Cl welchii* food-poisoning is caused only by heat-resistant, non-hæmolytic strains Nor can it be assumed that the causal organisms, even when they are fully heat-resistant, were necessarily present in the food before cooking Hobbs et al,[2] for example, refer to two outbreaks caused by typical hæmolytic strains that were only feebly resistant to heat Strains of *Cl welchii* of all kinds are very widely distributed in dust, including the dust of hospital kitchens McNicol and McKillop suggest that boiled fowls sitting in their own broth in a large container in a hospital kitchen are often exposed to invasion by dust-borne *Cl welchii*, for which boiled fowls in broth is an excellent medium This explanation agrees with that of McClung,[1] who emphasised that the cause of trouble in the outbreaks he reported was not lack of refrigeration but failure of the pans of food to cool quickly enough to a safe temperature Dische and Elek[5] showed that not all strains of *Cl welchii* cause food-poisoning, otherwise we might experience much more trouble of this kind

McNicol and McKillop suggest two ways of reducing the risk both from heat-resistant *Cl welchii* already in the chickens and able to survive cooking and from strains that might gain access after cooking From both these sources the risk could be curtailed and perhaps removed by cooking the chickens in a pressure-cooker and keeping them sterile by not opening the cooker until the chickens are to be served If this procedure is unacceptable, the cooked birds should certainly be taken from the broth as soon as possible after boiling and cooled in a place protected from dust—preferably being put into a refrigerator at the first possible moment To ensure that they cool quickly they should be well separated from each other—on a shallow tray, for example, as recommended by Norval and Collee,[6] who found that slowly cooled steak pies were admirable culture media for *Cl welchii* If, through forgetfulness or unawareness of risk, the birds are allowed to remain overnight in broth unprotected from dust and in a mass which cools slowly, diarrhœa may result

ANÆSTHESIA IN THE NEWBORN

ANÆSTHESIA for major operations in the newborn is associated with special difficulties Rees[7] believes that, the respiratory system being relatively immature, controlled ventilation at a high rate is indicated, and that this can be carried out satisfactorily provided that blood-loss is made good and a muscle relaxant is used The choice of relaxant is important, since the newborn child is sensitive to agents, such as *d*-tubocurarine chloride, that do not depolarise, yet relatively resistant to those that do[8] Suxamethonium is thus the agent of choice, but, as Rees points out, sensitivity to agents that do not depolarise may go hand in hand with a dual response to those that do, and long-continued administration of suxamethonium may be followed by depressed respiration This depression can be offset by neostigmine, but it is best avoided or at least decreased by carefully regulating the total dose of suxamethonium In adults the easiest way to keep the blood-suxamethonium at the minimum necessary level over a long period is to administer it by continuous intravenous infusion, but in a child this would require infusion of far too great a volume of fluid, and intermittent injection is essential This, by contrast with continuous infusion, is likely to call for a far greater total amount of suxamethonium, and small and frequent doses should be given in order, as far as possible, to mimic continuous administration

Intubation of the trachea is essential not only because of its importance for controlled ventilation but also because of the difficulty otherwise of maintaining a satisfactory airway Passage of the tube may be technically difficult when congenital abnormalities are present—especially micrognathia, in which the tongue is held back on the posterior pharyngeal wall by the underdeveloped lower jaw, and subglottic stenosis, which cannot always be discovered before intubation is attempted Since such factors are likely to prolong the act of intubation, Rees recommends that this should be carried out before anæsthesia is induced and without the aid of a muscle relaxant Thus, moreover, the danger that vomit may be aspirated is curtailed

Rees has calculated, on the basis of figures from the Liverpool area, that in the United Kingdom each year some 2000 newborn babies may need major operations—which suggests that these and other anæsthetic problems in the newborn are common enough to merit special study

DR ROBERT PLATT has been re-elected president of the Royal College of Physicians of London for the coming year

MR E M T FIRTH has been appointed Registrar General in succession to Sir George North, who is to retire on April 30 Mr Firth has been under-secretary and director of establishments at the Ministry of Health since 1947

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[2] Hobbs B C, Smith M E Oakley C L, Warrack, G H, Cruickshank, J C *J Hyg, Camb* 1953, 51 75

[3] Smith J Wallace J M *Hlth Bull (Edinb)* 1956, 14, 31

[4] Dickie, G G, Smith J *ibid* 1957, 15 81

[5] Dische, F E, Elek, S D *Lancet*, 1957, ii, 71

[6] Norval J Collee, J G *Scot med J* 1957, 2, 427

[7] Rees, G J *Brit med Bull* 1958 14 38

[8] Stead A L *Brit J Anæsth* 1955, 27, 124

Special Articles

RESPONSIBILITIES IN CEREBRAL PALSY

Individuals, Society, and Voluntary Agencies

E ELLIS
M D Cantab , D C H
MEDICAL DIRECTOR OF THE PERCY HEDLEY SCHOOL FOR SPASTIC CHILDREN, NEWCASTLE UPON TYNE

CEREBRAL palsy is not a new discovery, but it has aroused general interest in this country only in the past twelve years In the north of England fresh impetus was given to the study of cerebral palsy when a special school for affected children was opened in Newcastle upon Tyne in 1953 The management committee of this school appointed a medical director to

(a) Maintain an up-to-date register of children with cerebral palsy living in the five northern counties, from which it would be possible to determine the nature of the problems which cerebral palsy presents in this area, the number of children affected, and the facilities which should be provided for their care, education, and treatment,

(b) Establish an outpatient clinic for children with cerebral palsy where, in addition to the clinical examination of the child, an assessment could be made of the domestic and social circumstances in which the child lived, and the adjustment of the child and other members of his family to their circumstances,

(c) Keep the work of the school and the clinic constantly under review, so that the emphasis of the work could be altered to meet the needs of the five northern counties

This paper, therefore, is based on experience gained during the past five years in the north of England

There is some evidence that the incidence of cerebral palsy in this country has risen in recent years Ingram (1955) has suggested that the higher incidence of cerebral palsy which he found in Edinburgh in the period 1944–49, compared with the period 1938–43, was due not only to improvements in infant care in the neonatal period but also to survival of infants after illnesses which would formerly have been fatal The infant-mortality rate in England and Wales fell steadily from 150 per 1000 in 1900 to 23 in 1957 It seems inevitable that, along with this tremendous saving of infant life, a number of brain-injured children, who would previously have died, are now helped to survive, and that cerebral palsy is part of the price which the community must pay for the considerable improvements which have taken place in obstetric and pædiatric practice in the past fifty years

It is now generally agreed that cerebral palsy is a comprehensive term, covering a large number of conditions, with a variety of ætiological factors Knowledge about these factors has increased very slowly in the past century, and it seems unlikely that any spectacular advance will result from further retrospective studies Useful information may, however, be accumulated from long-term prospective studies Meanwhile, pressing problems are presented by those who suffer from cerebral palsy, and its management calls for careful attention If cerebral palsy is part of the price which the community must pay for improved obstetric and pædiatric care, how must the price be paid ?

Individuals

Parents

Cerebral palsy implies delayed motor development, which in most children is first recognised by the parents The more severely affected the child, the earlier is the abnormality noticed As it is usually the parents who take their child to their doctor for advice, the parents may be considered the first link in the chain of management

It is the duty of the doctor to explain the significance of the diagnosis to the parents and to advise them about the management of the condition It remains the parents' responsibility, aided by this advice, to care for their child at home day by day and year by year Theirs indeed is often a hard task They must maintain their understanding and their interest, in the face of an increasing physical burden and of their anxieties for the future They will always have to accept more than normal responsibility for their child If they can do so, they can help him to make the most of his disabilities If they are overwhelmed by their burden, if they neglect or abandon their child, he is indeed " deprived ", not only of a normal home life, but of the chance of ever living outside the artificial atmosphere of an institution It may well be said that the most important factor in the life of a young disabled child is the attitude of his parents to his disability

Doctor

The doctor must help the parents to play their most important role by bringing them gradually to understand, and later to accept, the full significance of the diagnosis He must always be available to give explanation and advice as each new situation is encountered

A hospital specialist who has a particular interest in cerebral palsy is usually the doctor who should give most of the initial explanation and advice He, too, may best be able to advise about treatment, while at a later stage a school medical officer can help with educational difficulties The advice of several specialists may be needed, about the child's vision, his hearing, or his intelligence, but for most parents their family doctor, because he is the doctor who knows the family best, is the doctor best qualified to give them continuing help, and he should remain as a link, interpreting the experts to his patients

Therapist

As interest in cerebral palsy becomes widespread, the diagnosis can be made at an increasingly early age As knowledge slowly accumulates, it is becoming accepted that a large proportion of those with cerebral palsy have only limited intelligence The challenge to the therapist at the moment is to find a way of helping young children and backward children, as well as older children of normal intelligence

The word treatment, applied to cerebral palsy, is potentially dangerous, because to many parents treatment implies a prospect of cure, and this blinds them to the incurable nature of the condition Therapists who wish to help children with cerebral palsy must have a clear understanding of the way in which a normal infant develops Only then will they be able to recognise abnormal development The study of the normal infant should lead on to a study of the abnormal movements in children with cerebral palsy The mechanisms which control these abnormal movements are set below the cortical level These mechanisms can therefore be used or modified by the therapist in young children, or mentally defective children, who are unable to cooperate, but for the achievement of voluntary control of fine or complicated movements intelligent cooperation by the patient is necessary

Therapists must not concentrate on motor development alone Because children with cerebral palsy move very little, their knowledge of their environment is limited

Sensation, or sensory perception, may be abnormal, so that the young child lacks the normal stimuli which are necessary for normal intellectual development Whether this delay by deprivation can ever subsequently be corrected remains in doubt, but it seems logical to widen the sensory experience of young children with cerebral palsy, not only by encouraging normal movements, but by using suitable toys and materials such as dough, plasticine, sand, and water At this point the therapist is trespassing on the preserves of the nursery-school teacher, but instead of regarding the two individuals as having separate functions, it would be preferable to regard them both as encouraging a single process of continuing motor and sensory development This approach to the management of cerebral palsy, which is strange to many therapists trained by conventional methods, calls for much observation and study, but it may yield results in cerebral palsy of all grades of severity and at all ages

It would be unfortunate indeed if, as the result of so much specialisation, the therapists came to regard themselves as experts essential for treatment It is not uncommon for children to be brought frequently from distances to attend crowded treatment departments, where their mothers are given a seat in a waiting-room while the child receives the expert attention of the therapist in an inner room This method of treatment may be the result of a constant urge to do something for the child In many cases it may meet to some extent the emotional needs of the parents, but far better that the time should be spent with the mother or father explaining the ways in which they can modify their child's development at home By teaching the parents in this way the therapists can ensure daily help for the child By taking the parents into her confidence the therapist can lessen their sense of frustration and can substitute for it a sense of achievement and pride in their child's progress

Society

Welfare Services

One of the results of cerebral palsy is social isolation The affected child is prevented by his disabilities from making normal contacts with other children and is thrown back upon the resources of his parents and his family Because their child is so abnormally dependent upon them, the parents themselves become socially isolated Recreation away from their home, either during the evenings or at holiday times, may be impossible for them This is a particular strain on the mother whose daily routine ties her to her home

The presence within a family of a severely disabled child may place a great strain upon the bonds which unite the family If these children are to benefit from home life, the break-up of their families must be prevented Even in the welfare state it is impossible to find for the disabled child an adequate substitute for home care

Cerebral palsy must therefore be recognised, and accepted by the community, as a social problem, so that appropriate welfare services, such as social clubs and holiday homes for affected children, and home helps or sitters-in for their parents, can be provided to meet the real needs of these children and their families The alternative to providing these welfare services is to provide a series of residential nurseries, residential schools, and institutions, where the patient can live from the time in infancy when the diagnosis is made until the day in adult life when he dies This policy of segregation—of institutional care from the cradle to the grave—is not only economically unsound, but also emotionally and psychologically wrong for the child, his parents, and the community in which they live

Schools, Occupation Centres, and Institutions

To fit children with such a wide variety of motor, sensory, and intellectual disabilities into any educational system, it is clear that a wide variety of schools is needed The following type of provision was made in 1953 and 1954 for the 133 children of school age with cerebral palsy who lived in three representative local-authority areas in the north of England

Type of provision	*No of children*
At home	24 (*18%*)
Home tuition	4 (*3%*)
Normal school or open-air school	70 (*53%*)
School for the educationally subnormal	3 (*2%*)
Special school for children with cerebral palsy	17 (*13%*)
Private school	2 (*2%*)
Occupation centre	3 (*2%*)
Institution	10 (*7%*)
Total	133

53% were attending normal schools or open-air schools It may be argued that this is not an unreasonable figure, bearing in mind the fact that over half of all cerebral palsied children have only a mild motor disability If a child with a physical handicap can manage, and benefit from education, at a normal school, he would better do so than be admitted to a special school where he would be mixing with children more severely handicapped than himself Yet subsequent experience suggests that about a third of those children with cerebral palsy who were attending normal schools or open-air schools had specific learning difficulties or were so backward that they needed more individual help than their teachers could afford to give them

Only 2% of the 133 children of school age were attending a school for educationally subnormal children There is in the northern region, as throughout the rest of the country, a shortage of accommodation of all kinds for backward children, in special schools for the educationally subnormal, in occupation centres, and in institutions This shortage is a particular hardship to the cerebral-palsy population, because it includes a relatively larger number of backward children than does the rest of the population

Below is an estimate, based on the combination of motor disability and intelligence of the 133 children who lived in the three representative local-authority areas, of the provision needed for children of school age with cerebral palsy

	Percentage
Normal school or school for physically handicapped pupils	30
Class or school for the educationally subnormal	24
Occupation centre	8
Institution	8
Special school for children with cerebral palsy	12
Special occupation centre for children with cerebral palsy	18
Total	100

Special provision should be made for two types of cerebral palsied children Special schools are needed, admitting children with a combination of severe physical disability and normal intelligence This combination accounts for only 12% of all children with cerebral palsy, and it is unfortunate that these special schools have received so much publicity in recent years This publicity has obscured the great need to provide for the heavily handicapped child who, though trainable, is prevented by his poor intelligence from benefiting from any sort of education, and whose parents, if given some relief, can still manage to care for him at home This second type of special provision should be in a special occupation centre, equipped to care for, to train, and to treat backward children with severe physical disabilities

Although buildings have an important part to play in the management of children with cerebral palsy, it is not the buildings and the accommodation within them that matter, so much as the personalities of those who care for the children and who attempt to help their families Personalities are always more important than bricks and mortar, and personalities are particularly important in the management of children with cerebral palsy

Voluntary Agencies

Parents' Associations

Associations of parents of disabled children have three important functions

The first is to help its members to accept the inescapable fact of their children's disabilities Parents have a very important part to play in the management of their children, and they cannot be expected to play this part satisfactorily while they remain confused and frustrated Acceptance of the inescapable eases tension and enables the best use to be made of available resources

The second is to create a well-informed public opinion This in turn will ensure that official help will be forthcoming to meet the needs of all disabled children

The third is self-help in cooperation with local authorities Most local authorities are willing, but unable, to meet all the needs of the disabled Parents can help by providing additional facilities in schools and clinics

In the past ten years associations of parents of spastic children have sprung up throughout the country, until there are now in England and Wales over a hundred local parents' associations These associations have been quick to realise that publicity is a powerful weapon, and by means of their publicity they have achieved a nation-wide interest in cerebral-palsied children They have also been slow to realise that publicity, because it is so powerful, is also dangerous, particularly to themselves Many of the statements that have been published on behalf of the parents' associations have been inaccurate or over-optimistic There appears to be an urgent need to impress on some parents' associations some of the fundamental facts of cerebral palsy If the parents can be helped to accept these facts, they will be in a better position to help their fellow members and to create a well-informed public opinion

The parents' associations have used considerable initiative to raise large sums of money from a sympathetic public It is much easier to raise money for cerebral palsy than to spend it wisely, and much money may be wasted in providing facilities before the needs are accurately defined

Voluntary Societies

Although in recent years interest in cerebral palsy has spread widely, knowledge of the subject has lagged far behind, and many aspects remain unexplored Knowledge of its causes has advanced only a short way beyond the stage reached by Little (1862) nearly a century ago In the past fifteen years several attempts have been made to determine the size of the problems presented by cerebral palsy, and to plan what is needed for their management More recently several interesting methods of treatment have been used

The cause of cerebral palsy must be investigated in maternity hospitals and pathology laboratories Voluntary societies can assist these carefully planned long-term studies by means of research grants The management of patients with cerebral palsy must be investigated largely outside hospital and laboratories because it is concerned with the natural history of the condition and the effect which it may have on the child, his parents, and his family This type of investigation demands a flexible approach and is best conducted by clinical scientists, educationalists, and welfare workers, supported by a voluntary society with an interest in cerebral palsy It is probable that those who work in this way will be in the best position to collect information about the medical, educational and social problems which cerebral palsy presents, and to supply it to all who are interested in this branch of social service

Summary

As obstetric and pædiatric care has improved in this country, it seems likely that the incidence of cerebral palsy has increased Although prevention is important, management of the condition presents more pressing problems

The most important factor in the life of a young disabled child is the attitude of his parents to his disability Doctors, therapists, and teachers must help the parents to care for their children at home To overcome the social isolation which this entails, improved welfare services are needed

In this country there is still a shortage of accommodation in schools and institutions for backward children This is a particular hardship to the cerebral-palsy population which contains a large proportion of backward children More accommodation should also be provided in special schools and special occupation centres

In their concentration on the child and his disabilities, the parents' associations have tended to ignore the fact that the parents themselves often need as much help as their children

Much remains to be learned about the great variety of disabilities included in the term cerebral palsy The necessary inquiries can best be supported by voluntary societies having an interest in this branch of social service

I am indebted to Dr F J W Miller, reader in social pædiatrics in the department of child health, University of Durham, for much helpful criticism in the preparation of this paper

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HEALTH SERVICE ESTIMATES

THE estimated gross total cost of the National Health Service[1] in England, Wales, and Scotland in 1958-59 is £677,679,845, compared with £649,322,885 in 1957-58 Appropriations-in-aid are estimated at £146,967,415, compared with £103,991,920 (an increase of £42,975,495), bringing the estimated net cost to £530,712,430, compared with £545,330,965 in 1957–58 (a decrease of £14,618,535) The cost of the hospital, specialist, and ancillary services is estimated at £434,758,709 in 1958–59, compared with £415,272,655 in 1957–58 (an increase of £19,486,135), under this heading advances to boards' revenue accounts are estimated at £398,595,000, compared with £382,660,150 (an increase of £15,934,850) General medical, dental, pharmaceutical, and supplementary ophthalmic services are estimated to cost £190,350,110 in 1958–59, compared with £184,496,980 in 1957–58 (an increase of £5,853,130) Grants to local health authorities are estimated at £30,797,800—an increase of £1,808,800 on the £28,989,000 in 1957–58

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[1] Civil Estimates for the year ending March 31, 1959 Class V Heal Housing, and Local Government H M Stationery Office 9s

THE LISTER FESTIVAL

THE triennial Lister oration of the Royal College of Surgeons of England was given on March 28 by Sir Stewart Duke-Elder An account of it appears on page 781

In the evening, at the Lister festival dinner, Sir JAMES PATERSON ROSS, the president, said that the chief festivals of the college are named after John Hunter and Joseph Lister, “ the greatest of our forefathers ” Hunter by the experimental method had been the father of scientific surgery, but surgery remained dangerous and limited until Lister made it safe for the patient, and not until physiologists showed how the body reacts to operations was the patient made safe for surgeons Lister would be staggered by the increase in the scope of surgery since his time, and he would be bewildered by the intense activity of the college, which he knew as a quiet institution Setting, by its examinations, a scientific standard which benefits patients all over the world, the college had had to undertake postgraduate teaching because most medical schools are fully occupied with undergraduates It provided what amounts to an honours course in surgical specialties, and Lister would have approved its association with the University of London, whereby professors in the college are also teachers in the university Besides teaching, the college, through its research laboratories, had an eye to the future, and to the possibilities of preventive as well as curative surgery All this work could not be carried through unaided, and the President spoke gratefully of the many friends who believe in its cause—mentioning among others the benefactions of Sir Simon Marks and his associates, the Wellcome Trust, the Leverhulme Trust, the British Oxygen Company, Imperial Chemical Industries, Lord Nuffield, and Mr Edward Lumley The history of the college was such that it has no need to build for aggrandisement, but to be true to its heritage it must fulfil its trust

Sir James was responding to the toast of The College proposed by VISCOUNT CROOKSHANK The toast of The Lister Orator was given by Sir ARCHIBALD McINDOE, vice-president, who said that Sir Stewart Duke-Elder has earned and won more academic distinctions than any other man in British medicine, while the affection in which he is held would presently be shown by a celebration of his 60th birthday To the Institute of Ophthalmology, the love of his life, he had contributed a tremendous amount, and the institute in its turn had contributed a tremendous amount to the Commonwealth In his reply Sir STEWART said that he was proud to be chosen as orator, and glad also for the sake of ophthalmology—the subject in which Lister did his first piece of research

The guests were welcomed by Sir RUSSELL BROCK, vice-president, who had clearly left part of his heart in Australia, which must be visited if a surgical education was not to remain incomplete What the American in Nevil Shute's book said of Australian scenery—“ this is beautiful all right, by any standard in the world ”—was true, he felt, of every aspect of Australian national life

Sir CHARLES WHEELER, P R.A., comparing sculpture with surgery, said that sculptors are often asked “ What do you do if you cut away something you really want ? ”—to which the answer was “ we never do ” He wondered what surgeons did in such circumstances certainly the specimens of their work walking about the streets seemed to compare favourably with some modern pieces of sculpture Though many art schools now dispensed with anatomy, the Royal Academy, where William Hunter had been first professor of the subject, still believed in it they felt that holes cut in the human torso ought to be filled up Quoting Hamlet's passage, “ What a piece of work is a man the beauty of the world the paragon of animals,” Sir Charles added “ That is the material that you work on and we work on.” Knowledge was not enough there was need, too, of the mysterious something which art supplies In each profession there were those whose art transcends knowledge and makes for genius—having a sense of the whole drama of human existence One such was Lister

Public Health

FOOD-POISONING CAUSED BY CLOSTRIDIUM WELCHII IN COLD CHICKEN

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ALTHOUGH diarrhœa due to *Clostridium welchii* was first described over sixty years ago (Klein 1895) and attention has been drawn in recent years to food-poisoning caused by heat-resistant strains, this organism is not always sought even when an outbreak of diarrhœa in hospital is being investigated

The typical symptoms come on 8–20 hours after the infected food has been eaten (Hobbs et al 1953) and are highly suggestive though not pathognomonic If the necessary bacteriological examination is not undertaken, the outbreak is given some non-specific label such as “ hospital diarrhœa ”

One of us (E J McK) has investigated many cases of diarrhœa in hospital, and on five occasions in the past two years has noted a clear association between *Cl welchii* food-poisoning and cold chicken in the diet This hazard to patients in hospital is illustrated by the outbreak reported here

The Outbreak

Clinical Features

About 8 P M on Aug 6, 1957, 9 patients in a medical unit of thirty-nine beds developed a brief illness characterised by profuse diarrhœa and lower abdominal colic with disproportionately slight general upset. By the next morning all had recovered No specific therapy was given Diarrhœa was confined to the 15 taking light diet, among whom 9 were affected, the patients who ate special or ordinary diets were not affected The maid attached to the ward (case 16) also developed severe diarrhœa on the same evening The only item of food common to the patients and the maid was cold chicken, which was served at noon to those on light diet only The maid had eaten the chicken left over from the patients' lunch, and no samples of this food were therefore available for examination.

Bacteriological Investigations

On the morning of Aug 7, when the diarrhœa had almost completely settled, rectal swabs were taken from all 16 persons who had eaten the chicken

Each swab was plated directly on two horse-blood-agar plates and on MacConkey's medium Three tubes of Robertson's cooked-meat medium were then inoculated, followed by one tube of Robertson's cooked-meat medium with 10% sodium chloride and one tube of selenite-F medium One blood-agar plate was incubated anaerobically, all the other media were incubated aerobically One tube of Robertson's medium was boiled for fifteen minutes before incubation, and another for an hour, the third was not heated before incubation Previous experience has shown that positive results are obtained after fifteen minutes' boiling of the fæces in a few specimens when they are not obtained after the more usual hour's boiling

Next day the anaerobic blood-agar plates were examined for hæmolytic and non-hæmolytic *Cl welchii* Further strains were isolated by plating both the heated and the unheated tubes of Robertson's medium on to horse-blood-agar and incubating anaerobically The identity of all the cultures of *Cl welchii* was confirmed by showing that they produced α-toxin (lecithinase), and that this was specifically neutralised by *Cl welchii* α-antitoxin This test was done in tubes containing lecithovitellin prepared by the method of Macfarlane et al (1941)

Staphylococci were isolated from the Robertson's medium containing 10% sodium chloride by plating on to blood-agar and incubating aerobically Fluid cultures of suspected colonies were tested for the production of coagulase by a tube test with human citrated plasma All further references to *Staph aureus* or staphylococci in this paper denote coagulase-positive *Staph aureus*

The MacConkey's medium and the selenite-F medium were investigated in the usual way for intestinal pathogens None of the specimens contained salmonellas or shigellas

Non-hæmolytic heat-resistant *Cl welchii* was isolated from 11 and *Staph aureus*, in small numbers only, from 7 of the 16 rectal swabs examined (table I) Both hæmolytic and non-hæmolytic strains of *Cl welchii* were isolated from a large proportion of the cultures (12 of the 16) Of the 10 people with diarrhœa 8 had non-hæmolytic heat-resistant *Cl welchii* in their stools

TABLE I—NON-HÆMOLYTIC HEAT-RESISTANT *Cl welchii* AND COAGULASE-POSITIVE *Staph aureus* IN FÆCES OF ALL AT RISK FROM EATING COLD CHICKEN

Case no	Symptoms of diarrhœa	Heat-resistant *Cl welchii* (15 min or more at 100°C)	*Staph aureus*
1	−	−	−
2	−	−	−
3	−	+	−
4	−	+	+
5	−	−	−
6	−	+	+
7	+	+	+
8	+	+	−
9	+	+	+
10	+	+	−
11	+	+	−
12	+	−	−
13	+	−	+
14	+	+	+
15	+	+	+
16	+	+	−
Total	10	11	7

Serological typing of all the non-hæmolytic strains of *Cl welchii* isolated, including the proved heat-resistant strains, was carried out by Dr Betty Hobbs of the Food Hygiene Laboratory of the Central Public Health Laboratory at Colindale Of the thirty-six strains examined, thirty were untypable by the available sera Untypable non-hæmolytic *Cl welchii* was isolated from 12 of the 16 persons at risk, and non-hæmolytic heat-resistant untypable *Cl welchii* from 9, of whom 8 had diarrhœa From 2 of the 3 who carried heat-resistant *Cl welchii* without having diarrhœa, the organisms isolated were of different serological types—type 5 and type 8 Possibly these two typable strains may have been unconnected with the diarrhœa

The staphylococci isolated from seven of the sixteen specimens proved to be of a wide variety of strains (table II) and were present in small numbers only, being isolated from enrichment but never from direct cultures

A month after the outbreak (Sept 13), when there was no diarrhœa, rectal swabs were taken from 16 patients in the unit, irrespective of the type of diet they were eating Only 1 patient who had been in the ward during the outbreak was sampled during this second investigation This sample was taken to provide a control observation The results of these cultures differ strikingly from those examined at the time of the outbreak A heat-resistant strain of *Cl welchii* was found in only 1 of the 16 patients examined, and *Staph aureus* in only 2

TABLE II—ANTIBIOTIC SENSITIVITY AND BACTERIOPHAGE TYPE OF *Staph aureus* ISOLATED DURING OUTBREAK

Case no	Antibiotic sensitivity					Phage type
	P	C	T	St	E	
4	R	S	S	S	S	6w/7/75+
6	R	S	R	R	S	53 (1000×R T D)
7	S	S	S	S	S	N T
9	S	S	S	S	S	7+
13	R	S	S	S	S	47/53/75/77
14	R	S	R	S	S	7/53/75+ (1000×R T D)
15	S	S	S	S	S	N T

P, penicillin
C, chloramphenicol
T, tetracycline
St, streptomycin
E, erythromycin
N T, non typable
S, sensitive
R, resistant

Discussion

The clinical picture was typical (Hobbs et al 1953) About eight hours after the ingestion of pre-cooked meat there was a brief illness characterised by colicky lower abdominal pain and diarrhœa The motions were watery and unformed but contained no mucus, blood, or pus There was no pyrexia, and systemic upset, as usual, was minimal

In the healthy adult this illness is merely an inconvenience, but in those already ill it may be prostrating, if not fatal When the illness is mild it is usually settling before note is taken of it, and complete investigation, including the food, is seldom possible Even in the present outbreak, in which food-poisoning was suspected early, samples of the suspected food could not be obtained This appears to be a not uncommon experience (Dickie and Smith 1957)

Non-hæmolytic heat-resistant *Cl welchii* was isolated from 11 of the 16 people exposed in this outbreak, and 9 of the 11 strains were untypable with Dr Betty Hobbs' sera The proportion of those with diarrhœa from whom an untypable strain was isolated (80%) corresponds to the previously reported figures for *Cl welchii* food poisoning (89% by Hobbs et al 1953) and is in keeping with the results reported for experimental *Cl welchii* food-poisoning (97% by Dische and Elek 1957) It seems quite probable that this outbreak was due to an untypable strain of heat-resistant *Cl welchii*

In the present outbreak the only item of diet taken by all the 10 persons with diarrhœa was cold chicken, and, though we have no direct bacteriological proof, it seems likely that this was responsible for the food-poisoning Cold chicken has already been noted as a potential source of *Cl welchii* food-poisoning (McClung 1945)

It has not yet been possible to establish with certainty how and when the chicken is contaminated with *Cl welchii*, and this problem is at present being investigated

We found no evidence in laboratory experiments that chicken is a more favourable medium than other meat dishes for the growth of *Cl welchii*, but the methods of cooling and storing boiled fowls often provide suitable conditions for the growth of such organisms

After cooking, the chicken may be left to cool in the broth, the two of which together provide an admirable medium for the growth of any *Cl welchii* that survives cooking or may subsequently gain access This is especially so in large kitchens such as hospital kitchens where many fowls may be cooked at one time and left to cool together with the broth in one container The mass of recently cooked chickens maintains a temperature favourable to bacterial growth for many hours particularly if the container is left at room temperature During transfer from the cooking-pot to the cooling container and during cooling they are liable to be exposed to hospital dust, which is heavily infected with *Cl welchii* The risk could be reduced either by cooking the chickens in a pressure cooker and keeping them sterile in this container until the time for serving them or by removing the birds from the broth after boiling and refrigerating them immediately and well separated from each other on shallow trays

Though contaminated, the chicken usually appears to be perfectly acceptable when served, and is regarded as palatable, on occasions it appears to be slimy, but it has never been foul-smelling or frankly putrid Thus it is served and eaten without hesitation, and the remnants are usually eaten or discarded before the onset of diarrhœa Patients who are receiving light diet are particularly liable to be affected, for cold chicken is an important part of their diet, these are the very patients liable to be most upset by such an episode

When diarrhœa was present, a wide variety of strains of *Staph aureus* was found in the stools of 7 of the 16 persons examined, in the control period they were found in *only* 2 This is a considerable difference, but one of us (E J McK unpublished work) investigating many cases of hospital diarrhœa has observed that the incidence of *Staph aureus* in fæces is higher in patients with diarrhœa, whatever the cause, than in patients without diarrhœa We think that this is the explanation for our findings in respect of *Staph aureus* and we do not hold the staphylococci responsible for the diarrhœa

In the present investigation the use of rectal swabs proved satisfactory, and in this type of outbreak the rectal swab has much to commend it All the persons at risk were examined with great convenience and complete certainty, whether they had diarrhœa or not Investigation did not depend on the chance that a sample of stool would become available at a convenient moment and that someone would remember to send it for laboratory examination An investigation of all at risk was thus possible It may be that, as indicated by Hobbs et al (1953), the negative results in the 2 patients with diarrhœa were due to the use of rectal swabs, but we think that the completeness of the sampling justifies the use of this method

Summary

A brief outbreak of "hospital diarrhœa" is described It was due to heat-resistant *Clostridium welchii* carried by cold chicken

Hospital patients whose diet contains cold chicken tend to be those given light diet

These are the very patients in whom even a brief attack of diarrhœa may be particularly troublesome

Our thanks are due to Dr T N Fraser for allowing us to report this investigation of patients under his care, and to Dr Betty Hobbs for the serological typing of all the numerous strains of heat-resistant *Cl welchii* from this outbreak

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McClung L S (1945) *J Bact* 50, 229
Macfarlane, R G, Oakley, C L, Anderson, C G (1941) *J Path Bact* 52, 99

Scotland Increasing Mortality in Older Men

THE report of the Department of Health for Scotland[1] draws attention to the smudge on the generally satisfactory picture of that country's health while the death-rate is falling in all other groups, that in men in the second half of life is rising This increase cannot be attributed to the rising age of the population, and it means that some morbid process or processes must be on the increase At these ages "there are very few causes of death that do not affect males more than females", but the chief causes are the heavier liability of men to lung cancer and to cardiovascular disease, especially coronary thrombosis "Were it not for these two causes the male death-rate would be declining at approximately the same rate as the female although remaining at a higher level"

In Scotland the mortality from all causes in men aged 55-64 has risen over the past ten years, but in England and Wales the rate in this group has remained about the same, though the rate in men aged 65 and over has increased In England and Wales the rate remains much the same, though fluctuating, in women aged 75 and over, and has fallen in all other age-groups

The general improvement in younger people is exemplified by the infant-mortality rate, which in 1957 remained at the previous year's low record, the stillbirth and maternal-mortality rates, which were the lowest ever, and the tuberculosis death-rate (13 per 100,000, compared with 66 per 100,000 ten years previously) The number of notifications of tuberculosis rose from 5915 in 1956 to 7859 in 1957, because of the mass-radiography campaign, in which 1,319,867 people were radiographed

After cardiovascular disease and cancer, accidents caused most deaths in Scotland Bronchitis was the fifth commonest cause of death but caused most absence from work The influenza epidemic was a relatively benign one, but there were 90 deaths from it in one week—a figure rarely exceeded before Children's teeth continue to give cause for concern, at dental inspections of children aged 12, 20–30% of all teeth were recorded as missing, decayed, or filled

Outbreaks of Staphylococcal Infection

BECAUSE of staphylococcal skin infections in newborn babies, the maternity ward of the Southern General Hospital, Glasgow, is being closed There is no reason to believe that there is any connection with the outbreak in the Royal Maternity Hospital, Glasgow, three months ago, when 2 babies died[2] The ward is emptying gradually as patients become fit to be moved, no new patients will be admitted till the ward has been disinfected Castle Hill Maternity Hospital, Shaftesbury, Dorset, has also been closed and disinfected because of an outbreak of skin infection in babies[3]

Clean Air Act

THE Minister of Housing and Local Government has laid before Parliament regulations[4] setting out the exceptions to the ban on dark smoke[5] The exceptions are designed to allow for such essential operations as cleaning the fires of furnaces, which may necessarily involve emission of dark smoke for short periods Further regulations[6] add certain industries to those controlled by the Alkali Act rather than the Clean Air Act

River Pollution

THE Rivers (Prevention of Pollution) Act, 1951, required the consent of the Minister of Housing and Local Government before a river board might take proceedings under the Act for pollution caused by sewage or trade effluent This requirement was limited to seven years, but the report[7] of the trade effluents subcommittee recommends extension of the period by three years to 1961

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[1] Report of the Department of Health for Scotland for 1957, Cmd. 385 H M Stationery Office, 1958 Pp 150 7*s*
[2] *Scotsman* April 2
[3] *Liverpool Daily Post* April 2
[4] The Dark Smoke (Permitted Periods) Regulations, 1958 S I no 498 H M Stationery Office Pp 2 3*d*
[5] See *Lancet* Feb 15, 1958 p 371
[6] The Alkali, &c, Works Order, 1958 S I no 497 H M Stationery Office Pp 3 3*d*
[7] Ministry of Housing and Local Government First Report of the Trade Effluents Subcommittee of the Central Advisory Water Committee H M Stationery Office 1958 Pp 9 9*d*

Medicine and the Law

Diminished Responsibility

THE Court of Criminal Appeal gave its reasons for allowing the appeal of a labourer, aged 52, who was convicted of the capital murder of a 15-year-old boy The defences put forward were (1) that in killing the boy the accused was suffering from diminished responsibility as defined by section 2 of the Homicide Act, 1957, and was accordingly not guilty of murder but of manslaughter, (2) that the murder was not in the course or furtherance of theft (as alleged by the prosecution) so that even if the defence of diminished responsibility was not accepted the murder was not capital On March 24 the court allowed the appeal on the first ground and substituted a verdict of manslaughter[1]

The LORD CHIEF JUSTICE said that the second ground of appeal need not be considered and the court gave no decision on it The accused was a confirmed practising sodomite and there was evidence of some association between him and the boy, who was not seen alive after 4 30 P M on Nov 18, 1957, when he left a new job, having previously collected wages due to him from a former employer The boy's mother received three anonymous postcards, the first of which stated that the boy had gone to London as a woman was after him, the second that he was living in London with prostitutes, and the third that he was dead All three were written by the accused, who also wrote anonymously to the police to say that the boy's body was in the Tyne, and also accusing the boy of sodomy On the same day, he gave himself up to the police and described how he had killed the boy by smashing his head with a glass bottle filled with water and then with a claw hammer That was confirmed by postmortem examination The body was found cut in half and disembowelled and stowed in a sump under a boxing hall in Newcastle The accused, in a statement to the police, alleged that he had killed the boy because the boy was demanding money from him He also stated that he had killed the boy for his wages

On the issue of diminished responsibility none of the facts were disputed The defence called three medical witnesses Dr I G W Pickering, the senior medical officer of Durham Gaol, Dr R Orton, consultant psychiatrist at Newcastle General Hospital, and Dr T M Cuthbert, physician-superintendent of St Luke's Hospital, Middlesbrough, all three of whom had personally examined the accused The prosecution did not challenge the opinions they had formed All agreed that he was not insane within the McNaughten rules, but they were all satisfied that his mind was so abnormal as substantially to impair his mental responsibility, and gave their reasons for that opinion The evidence was clearly enough to shift the burden of proof thrown on the defence by section 2 of the Act of 1957, yet no medical evidence was given by the prosecution in rebuttal

What were the facts or circumstances which would justify a jury in coming to a conclusion contrary to the unchallenged evidence of those gentlemen? While emphasising that the decision in these cases, as in those in which insanity was pleaded, was for the jury and not for the doctors, the verdict must be founded on evidence If there were facts which would entitle a jury to reject or differ from the opinions of the medical men, the court would not, and indeed could not, disturb their verdict, but if the doctors' evidence was unchallenged and there was no other on that issue, a verdict contrary to their opinion would not be a true verdict in accordance with the evidence Here there was evidence of premeditation, but an abnormal mind was as capable of forming an intention and desire to kill as one that was normal, it was just what an abnormal mind might do The revolting nature of the crime itself would cause most people to say that it was the work of a maniac, and the court could well understand that a jury faced with such a crime committed by a sodomite would think that such a creature ought not to live, and that a verdict involving a capital sentence was the only one appropriate But Parliament had altered the law and decreed that if killing was committed by a person whose abnormal mind had seriously diminished his responsibility, the verdict was to be manslaughter and not murder The Criminal Appeal Act, 1907, directed the court to allow an appeal if they thought that the verdict of the jury should be set aside on the ground that it was unreasonable or could not be supported by the evidence Having regard to what they thought must have affected the minds of the jury the court would not care to say that the verdict was unreasonable, though they felt bound to say that it was not supported by the evidence The fact was that there was unchallenged evidence that the accused was within the provisions of section 2 of the Homicide Act and no evidence that he was not

REGINA *v* MATHESON *Court of Criminal Appeal* Lord Goddard, *C J*, Streatfeild, Slade, Donovan, and Havers, *JJ* April 1, 1958 George Waller, Q C, and Peter Taylor (registrar, Court of Criminal Appeal), P Stanley-Price, Q C, and R Rawden Smith (Director of Public Prosecutions)

E M WELLWOOD
Barrister-at-Law

Length of Pregnancy

A husband and wife resided in Kenya In December, 1954, they ceased to live together and the wife returned to England The husband spent a leave with her in England between April 22 and May 14, 1955, and sexual intercourse took place on the first or second night of that leave In the early morning of Dec 2, 1955, the wife gave birth to a 6 lb child at a nursing-home Subsequently the husband ceased to maintain the wife and she applied for an order against him on the ground of his wilful neglect to provide her with reasonable maintenance The husband alleged that he was not liable to pay maintenance since, inter alia, the wife had committed adultery with an unknown man in about February or March, 1955, as a result of which the child was born, he asked the court to infer that the child was not his as, after December, 1954, no intercourse had taken place between him and his wife save during the leave period, and the child was a normal full-time child without any signs of prematurity

Mr Justice COLLINGWOOD said that the matron of the nursing-home at which the child was delivered had said in evidence that she had no doubt that it was a full-time child The medical experts who had given evidence were in agreement as to the signs of prematurity but disagreed as to whether all or any of them would have been present

Dr C G Nairn, on behalf of the wife, had said that all or any of the recognised signs of prematurity would not be necessarily present in any one given case, and that none of them would invariably be present, that the textbook average of a 280-day period of gestation was reckoned from the onset of the last menstrual period but that the expected date of birth could not be worked out by reference to the date of sexual intercourse alone, and it was necessary to go back to the first day of the preceding menstrual period and add 280 days which would then give an approximate date of delivery at the best Dr Nairn's view was that to the 224 days (April 22/23 to Dec 2) 21 days could be added, that was a total of 245 days of fœtal life, and, where, as in the present case, there was evidence of irregularity in periods, he would add 26 days in the absence of definite evidence as to the presence of a menstrual period —which would bring the total up to 250 days He had said that assuming that there was a proper menstrual period and that 21 days only had to be added, a fœtus of 245 days duration would not necessarily be so premature as to be obvious, he would call it an eight-month child and from his experience it was impossible to distinguish an eight-month from a nine-month child with any certainty He agreed with *Taylor's*

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[1] See *Lancet*, April 5, 1958, p 736

Medical Jurisprudence[1] and with the evidence given by Dr Roques in *Clark* v *Clark*[2] where it was held that a child born 174 days after the earliest date when intercourse could have taken place could be legitimate Dr G H Dodds, who had been called for the husband, had not agreed with the statement in *Taylor* nor with the evidence of Dr Roques, she would not admit the possibility that the child could have been the result of intercourse on April 23, 1955, and yet show no signs of prematurity She agreed that it was permissible to add 21 days, but not that one must do so

The question for His Lordship was whether the medical evidence had satisfied him beyond reasonable doubt that the wife had committed adultery The answer was that it had not He could not disregard the evidence of a witness of the experience and status of Dr Nairn and accepting this evidence, he was satisfied that the child born on Dec 2, 1955, could have been the result of intercourse on April 22/23, 1955

Burgess *v* **Burgess**—*Probate, Divorce and Admiralty Division* Collingwood, *J* March 27, 1958 R A J Temple, Q C, David Henderson & Kevin Winstanley (Bracewell & Leaver) James Stirling, Q C, and John Syms (Gordon Dadds & Co)

E JONES
Barrister-at-Law

Parliament

Disabled Persons (Employment) Bill

ON March 31 Mr ROBERT CARR, parliamentary secretary to the Ministry of Labour and National Service, in moving the second reading of this Bill, said that its purpose was to implement the few recommendations of the Piercy Committee on the rehabilitation, training, and resettlement of the disabled[3] which required legislation It was a small Bill because the committee had come to the conclusion that the statutory framework of the services was basically satisfactory and had centred their recommendations on how the services could be more effectively used The main provisions of the Bill are as follows

The minimum age for attendance at vocational training courses and industrial rehabilitation courses is reduced from 16 to the school-leaving age Courses will thus be available for boys and girls immediately on leaving school, and the present gap will be avoided

The minimum period of disability before a person becomes eligible for registration is increased from 6 months to 1 year

The powers and duties of the local authorities for the employment and training of the disabled are transferred from the jurisdiction of the Health Ministers to the Minister of Labour The local authorities' responsibility for welfare and aftercare will remain under the jurisdiction of the Health Ministers as at present

In the debate Mr SOMERVILLE HASTINGS said that he was uneasy that these services should drop the pilotage of the Ministry of Health He appreciated that the change would be administratively convenient, but disability was largely a medical problem and he thought that it would be to the advantage of the disabled if there were always a watching brief on health available to them In their training, in the selection of occupations for them, and in the supervision of their progress, recovery, and capacity for new work, medical considerations must always come in He hoped that under the new arrangements this would not be forgotten

In his closing speech Mr CARR gave an assurance that the local-authority services would not be covered by the block grant, but would remain direct-grant aided

QUESTION TIME

Children in Mental Hospitals

Mr N N DODDS asked the Minister of Health what was being done to establish small units throughout the country for giving treatment to children who are acutely ill so as to eliminate the need for placing them in mental hospitals primarily devoted to adults, and sending them so far away as to deprive them of visits by relatives and friends—Mr DEREK WALKER-SMITH replied There are 17 special units for mentally ill children in England and Wales 10 of these are administered in association with a mental or neurosis hospital, all these are in buildings separate from those used for adult patients 9 other units are planned or under consideration Because the number of children who suffer from mental illness (as distinct from mental defect) is fortunately comparatively small, admission to a special unit may involve sending them farther from home than would admission to the mental hospital serving the area in which they live

Mr DODDS asked the Minister what consideration had been given to ending the detention of children at Rampton Mental Hospital—Mr WALKER-SMITH replied Alternative arrangements are not available for these children who are of dangerous or violent propensities They are transferred to other care as soon as this is warranted by improvement in their condition

Review of Mental-defective Patients

Mr DODDS asked the Minister what progress had been made in reviewing the cases of mental-defective patients with a view to ending compulsory powers, consequent upon the instructions issued on Jan 16—Mr WALKER-SMITH replied At March 25 hospitals had submitted 9122 recommendations and of these 5155 patients have been discharged from orders to remain in hospitals on an informal basis

Merit Awards

Mr KENNETH ROBINSON asked the Minister of Health the total numbers of consultant physicians, surgeons, and psychiatrists in England and Wales, and what was the number of merit awards in each of the three categories, showing A, B and C awards separately

Mr WALKER-SMITH replied On Dec 31, 1957, the figures were as follows

Specialty	Number of consultants	Awards			
		A	B	C	Total
General medicine	822	59	151	263	473
Mental health	614	6	20	63	89
General surgery	863	62	138	256	456

NOTE If a consultant practises in more than one specialty, he has been included in each.

Poliomyelitis Vaccine

Mr S S AWBERY asked the Minister if the supply of poliomyelitis vaccine and Salk vaccine was now sufficient to meet British requirements, what proportion of schoolchildren had so far been inoculated, and when he expected 100% to be inoculated—Mr WALKER-SMITH replied Purchases of poliomyelitis vaccine, including Salk, are being kept under constant review in the light of the number of registrations for vaccination Separate figures for schoolchildren are not available, but at the end of February 37% of all the children in Great Britain who had been registered had had two injections and a further 11% their first injection It is the Government's aim that vaccination should be available by the summer for those in the priority groups who have registered

Mr R S RUSSELL asked the Minister if he would arrange for local authorities which had more anti-poliomyelitis vaccine than they needed at the moment to transfer some to those which did not possess enough for their immediate needs—Mr WALKER-SMITH replied While no authority has more vaccine than is needed to vaccinate its registered children, I am aware that some authorities which at present have vaccine in hand are giving others temporary assistance by mutual arrangement, and I am encouraging this Of the total quantity of vaccine issued to date 62% has been of British manufacture

Cost of Antibiotics

Mr A M SKEFFINGTON asked the Minister why the one firm supplying specialised antibiotics was not subject to cost investigation —Mr WALKER-SMITH replied Some 15 firms supply specialised antibiotics to the National Health Service, and, of these, 2 firms are each the sole supplier of one particular drug For the supply of these two drugs to hospitals the Ministry of Health negotiates running contracts, which do not provide for cost investigation because the firms have so far been unwilling to accept a costing clause and I have no power to compel its inclusion

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[1] 11th ed vol 2, p 34

[2] (No 1) (1939) P 228, 234 See *Lancet*, 1939 i, 593

[3] See *Lancet*, 1956, ii, 986

Regional Hospital Expenditure

Mr R L MAWBY *asked the Minister whether he would indicate in a table, for the financial years* 1952–53 *to* 1957–58, *the expenditure, actual or estimated, for capital and for all other items together respectively, of the hospital authorities per head of the estimated population for each hospital region of England and Wales, including therein the expenditure of boards of governors as well as those of regional hospital boards* —Mr WALKER-SMITH The following table sets out the information

Region	Capital expenditure per head of population					
	1952–53	1953–54	1954–55	1955–56	1956–57	1957–58 (estimate)
	s d	*s d*	*s d*	*s d*	*s d*	*s d*
Newcastle	4 8	4 1	8 1	5 9	7 5	10 7
Leeds	4 0	3 10	4 4	4 4	5 4	7 2
Sheffield	3 1	3 6	4 5	5 7	6 8	7 8
East Anglian	4 10	4 5	5 2	5 4	5 10	6 8
N W Metropolitan	5 5	5 0	5 11	5 10	6 4	7 10
N E Metropolitan	4 3	2 10	3 9	3 5	4 8	6 11
S E Metropolitan	4 0	3 10	4 6	4 3	7 1	8 3
S W Metropolitan	4 9	4 10	5 9	6 4	7 2	7 9
Oxford	4 2	4 4	8 0	8 0	9 9	14 5
South Western	3 9	3 6	5 11	4 11	6 4	8 7
Welsh	5 2	6 1	7 5	6 8	7 10	10 4
Birmingham	3 3	3 4	3 7	3 10	4 11	6 10
Manchester	3 9	3 3	3 3	4 3	4 8	6 3
Liverpool	3 9	3 5	5 0	6 0	8 7	11 0

Region	Revenue expenditure per head of population					
	1952–53	1953–54	1954–55	1955–56	1956–57	1957–58 (estimate)
	£ *s d*	£ *s d*	£ *s d*	£ *s d*	£ *s d*	£ *s d*
Newcastle	4 9 10	4 17 2	5 0 7	5 9 9	6 0 8	6 10 3
Leeds	4 19 0	5 2 7	5 8 5	5 17 8	6 9 5	6 19 5
Sheffield	4 1 7	4 5 5	4 10 0	4 18 2	5 7 10	5 15 4
East Anglian	4 4 9	4 9 0	4 13 7	5 3 0	5 12 9	6 0 5
N W Metropolitan	7 7 0	7 12 1	7 17 2	8 9 4	9 1 7	9 12 7
N E Metropolitan	6 16 11	7 4 4	7 8 2	8 0 2	8 12 10	9 2 1
S E Metropolitan	7 0 3	7 4 8	7 10 5	8 1 11	8 14 8	9 5 8
S W Metropolitan	7 4 4	7 10 5	7 15 2	8 9 1	9 2 11	9 14 2
Oxford	5 11 0	5 17 0	5 19 8	6 9 6	6 18 10	7 5 7
South Western	5 15 9	6 1 8	6 5 5	6 17 4	7 9 0	7 17 10
Welsh	4 17 6	5 5 7	5 11 4	6 1 7	6 14 8	7 3 11
Birmingham	4 11 4	4 15 3	4 19 11	5 7 10	5 17 0	6 4 5
Manchester	4 12 0	4 17 1	5 0 9	5 10 5	6 1 6	6 9 2
Liverpool	5 12 5	5 18 6	6 4 4	6 14 11	7 6 3	7 16 6

In *some regions more than in others revenue expenditure is increased* by the provision of services, at teaching or non-teaching hospitals, for patients from other regions No estimate is, however, available of the effect of this upon the figures

National Health Insurance Contributions

Mr FRED BLACKBURN asked the Chancellor of the Exchequer by how much the weekly contributions for National Insurance and Health could be reduced if such contributions ceased to rank for tax relief —Mr D HEATHCOAT AMORY replied By about a shilling in the case of a male employee over 18, on the assumption that the extra revenue was devoted to the National Insurance Fund

Nursing at Mental Hospitals

The rate of recruitment of nursing staff to *mental* and *mental*-deficiency hospitals has improved in the last two years with an increase in the number of both men and women students The figures are as follows

—	1955	1957	Increase
(*a*) *Total nursing staff*			
Whole-time	26,713	28 443	+1730 (*6*%)
Part-time	9130	9953	+ 823 (*9*%)
(*b*) *Student nurses* (*included in* (*a*))			
Whole-time—Male	1708	2426	+ 718 (*42*%)
,, Female	2518	3277	+ 759 (*30*%)

In England Now

A Running Commentary by Peripatetic Correspondents

I SUPPOSE histories are a good thing I recall Sir Luke telling us when we were boys "Pay attention to the anamnesis, gentlemen, and the rest follows as the night the day" To him (and also to all neurologists I have since met) the physical signs could be made to support any diagnosis the history had suggested Perhaps it was this fact that decided me, in later life, not to pay too much attention to the patient's utterances, which are, after all, subjective, highly coloured, and possibly implanted by his wife, the neighbours, or his study of the Sunday newspapers To me the honest physical sign was everything, I spent long hours seeing if the patient knew which way I was moving his toes (holding only the lateral aspects, of course) I decided that a good laboratory test was worth an hour of talk and I always had an excuse for the lab if they baulked at doing the ketosteroids just *once* more The genetic mutations that must have resulted from my X rays now appal me

But as old age creeps on and the chromium plate is quite worn from the margins of my stethoscope, I must confess to a certain lethargy—a disinclination to budge from the comfort of the armchair "Tell me all about it," I say and fill my pipe I feel disgruntled when obliged to lay stethoscope on chest "No need to take all that lot off, old chap," I say, listening through his waistcoat Very reprehensible, I know, but I reckon I'll live longer, though I suppose there's a chance my patients won't Still, I do think I used to overdo the examining side of things in the old days It heartens me to see these studies of observer error makes me remember all sorts of times when different physicians heard different murmurs in the same patient after all if radiologists differ on shadows why shouldn't the stethoscope lead to dispute? When Sir Luke said "A diastolic murmur, boy, can't you hear it?"—he may have heard one, but that doesn't mean it was actually there

The final vindication of my new outlook came from a couple of cases I heard of recently The first was a young lady who had been through the mill at some fertility clinic to the extent of having air pushed around (with normal results) Some time afterwards a psychiatrist suggested that her sterility was probably due to the fact that she had not had sexual relations for some years The other one was a young man with exceptionally large masseters diagnosed as an atypical variant of pseudohypertrophic muscular dystrophy Long were the conferences and a muscle-biopsy was done but was normal Legend has it that the new H P asked the chap "What do you do when you're worried?" "I clench my teeth very tight, Doctor," he said Yes, I think Sir Luke was right all the time

* * *

The peripatetic discovery (March 29) of a single pedal, in a good state of preservation, lying on a public highway has excited the interest of bicycle historians everywhere As I see it, the circumstances point to the pedal having become detached from the machine at a moment when the rider's foot was not in contact with it Otherwise he could hardly have disregarded its loss

It therefore becomes of vital interest to know the gradient of the road at the site of the find For if the pedal was lying, as one must hope it was, half-way down a good long hill, its presence there could be regarded as presumptive evidence of the survival of at least one member of a species of cyclist which all the most recent authorities have presumed to be extinct in this country, though occasional specimens were still to be found earlier in the century—mainly, for some unexplained reason, among country clergy I refer, of course, to that type of rider who, scorning (or perhaps distrusting) the new-fangled "free-wheel", was forced while coasting downhill to disengage his feet from the pedals and rest them temporarily on brackets attached for the purpose to the front fork The loss of a pedal unbeknown to the rider at such a time is readily attributable to the exhilaration produced by the downward rush, while even if he were conscious of it, his failure to stop and retrieve the component so vital to his progress beyond the foot of the hill may be explained by the fact that a fixed wheel was, in this species, usually associated with rudimentary brakes, if not with their total absence

If, on the other hand, the find was made on a level stretch, one is forced back on a more prosaic explanation Tuberculosis of the knee-joint in early life had left the cyclist with one stiff leg, forcing him to rely for propulsion on the unaided efforts of the other When, therefore, the unused pedal fell off one day, its loss left him unmoved As a matter of fact the thing was always getting in the way of his lame leg and he had been meaning for months to take it off anyway, only he could never find that damned spanner

* * *

Rural sanitation is full of surprises, the conditions in and around shallow wells, for example I was inspecting drainage and water arrangements at a country house last week and noticed that the shallow well which was the sole supply of drinking-water had a well cover raised about 2 ft above ground level on top of a concrete wall, and that the ground for some distance around was adequately concreted, thus excluding surface contamination of the well The well cover was unusually high, but nevertheless I congratulated the house-owner on his initiative and hygienic standards, only to be told that the work had been done by the previous owner of the house, not in the interests of hygiene, but to provide himself with a mounting-block!

* * *

The Mandarin's sudden appearance for a consultation was an unusual event in our Thames Valley backwater His card bore a West-end address and "late of Peking" with, I presume, his name and "Sweet Flowering Twig" in brackets for the benefit of those ignorant of Pekinese, or more probably High Manchu His high-pitched voice told me he was seventy-eight and that his name was McConachie He could easily have been ninety

A glance at his face, like dried-out putty, his pin-point pupils, his emaciation, and I saw his whole case-history in a flash Unable to obtain heroin, cocaine, and the like in his own milieu, he was travelling afield in his remarkably fine Bentley (with an even more remarkable blonde) pleading intractable sciatica—a shot of pethidine plus script for two dozen ampoules would tide him over the weekend party at Henley I saw him in his red and gold bedragoned robes, long mustachios adroop, moist napkins pressed to his brow, the gold nail-shields removed to scoop more easily his winnings at Fan Tan (does anyone play Mah Jong?), twitching his ivory fan, whilst the bead curtains silently parted to disclose the youngest tea concubine I saw his short pigtail by which the spirits would whisk him to transports of celestial delight when mortal span had ceased, and, brooding over all, the inscrutable East—the Winter Palace, the Last Empress, Somerset Maugham, and Fatalism

But there he was, alive and kicking off his sandals Emanating a faint whiff of burning joss-stick, with hands clasped and hidden in his sleeves, he bowed low and slow from the waist, and—Confucius bless him—paid me half-a-guinea for my diagnosis, prescription, and prognosis of his athlete's foot

* * *

I rang the boy on the office phone The typist answered

"Is Jackson there?"

"I'll send him in" And before I could say more, she had put down the phone

A moment later Jackson appeared

"I didn't mean her to send you in," I started apologetically "I just wanted you on the phone" But Jackson had disappeared A moment later the phone rang

"Jackson here"

* * *

A bright young thing in whom a possible diagnosis of glandular fever had been raised—and the necessary investigations ordered—asked with a blush on the next ward round whether her Beau Brummell was positive

Letters to the Editor

PRE-ECLAMPTIC TOXÆMIA

SIR,—In his ingenious explanation of the ætiology of pregnancy toxæmia, Professor Platt (March 15) invokes an antigen-antibody reaction between fœtus and mother —"the condition being akin to rhesus incompatibility in reverse"

The kidney has been shown to be involved in antigen-antibody reactions

Pressman[1] has confirmed earlier findings that all available types of antisera are capable of nephrotoxic action After the injection of antistreptococcal serum impregnated with radioactive iodine, radioactivity was found only in the glomerulus, none being transported into the tubule This evidence of ischæmic spasm of the renal cortex is supported by Hartman's[2] demonstration that injection of an anti-cortex serum, which he attributes to spasm of the renal afferent arteries, reduces the number of glomeruli in the kidney—a happening that may explain the ultimate anuria consequent on renal homotransplants There is also much evidence that renal cortical ischæmic states can account for "toxæmic" manifestations[3]

I believe, however, that Professor Platt's hypothesis is untenable for several reasons It does not explain (1) why toxæmia is pre-eminently a disease of the primigravid, (2) how it can occur post partum, or (3) why it should sometimes recur at labour, days after subsiding on the death of the fœtus Furthermore there are two possible sources of error in the compilation of the statistics—first the insistence on the eventual presence of albuminuria for the diagnosis of toxæmia, and secondly an implied acceptance of the equal accuracy of diagnosis in the two generations—an equality disturbed by medical awareness of the condition and the greater facilities for antenatal supervision in the younger

By their findings, Professor Platt and his colleagues exclude the possibility that only one gene is responsible for pre-eclampsia, but they still think that several different genes may be capable of causing the disease There is recent proof, however, that this cannot be so

The failure of renal homotransplants to take seems to be based on a specific immunological reaction Such a reaction is absent in identical twins, for renal homotransplantation has been effected in three sets of identical twins (Merrill[4]) In the light of this, a case-report just published by Brown[5] needs scrutiny

It concerns a first pregnancy, with identical twins, which was entirely normal up to the 20th week From then until the 24th week the patient had acute hydramnios and "imminent" eclampsia Rational treatment by amniotomy overcame the excessive uterine stretch, and the signs of toxæmia subsided The hydramnios did not recur and the pregnancy continued for a further 16 weeks perfectly normally At birth one twin was in a papyraceous state its length of 15 cm indicated that it had perished much before the 24th week The structure of the placenta and the single sac showed that the twins were identical

If there had been any particular genes in the fœtus papyraceus responsible for the pre-eclampsia, the same genes, in the surviving twin, would have perpetuated the toxæmic process The disappearance of the toxæmia excludes a genetic intrusion into the ætiology

This case is, I believe, sufficient to refute Professor Platt's thesis—unless perhaps he argues that his hypothetical factor, which may protect the mother after her first toxæmic pregnancy, can develop on the intrauterine death of one twin

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[1] Pressman D Fifth Annual Conference on Nephrotic Syndrome Philadelphia, 1953

[2] Hartman, M E *Arch Path* 1957, 64, 679

[3] Sophian, J *Excerpta med* 1958, 11, sect x, 1

[4] Merrill, J P Address to the Renal Association London, 1957

[5] Brown, G R *J Obstet Gynæc Brit Emp* 1958, 65, 61

London, W 1 JOHN SOPHIAN

SIR,—My interest in the paper by Professor Platt and his colleagues prompts me to ask whether they would be kind enough to furnish the following further particulars

(1) How many of the women graduates or wives of graduates had had their blood-pressure taken before pregnancy?

(2) At what stage of pregnancy the hypertension, the hypertension+proteinuria (H+P) or the hypertension+œdema (H+O) developed?

(3) Whether the 8 women who had toxæmia in their second pregnancy had it in their first, and

(4) The perinatal mortality associated with the "pre-eclamptic toxæmia"?

It is indeed strange that at a time when well-conducted antenatal clinics are able virtually to abolish eclampsia the term pre-eclampsia should remain so fashionable Apart from causing maternal death or damage, or fœtal death or damage, "pre-eclampsia" possesses a merely academic interest Leaving hypotheses aside we have found at Bradford that the perinatal mortality associated with hypertension, whether essential or occurring during pregnancy (about 2500 cases) was between 5% and 6%, with H+O the same, with H+P, 20%, and with eclampsia approximately 50% Further, our figures show conclusively that the earlier the onset of H+P during pregnancy the more likely will be the mother to have either hypertension or H+O or H+P in subsequent pregnancies A woman who develops acute eclampsia during the 39th or 40th week of pregnancy will most likely remain normal throughout subsequent pregnancies, whereas a woman who develops H+P at or about the 34th week of pregnancy in two successive pregnancies, notwithstanding adequate antenatal care, is incapable of a normal pregnancy apart from denervation of her internal iliac vessels or some form of sympathectomy It is, therefore, essential to differentiate these types of cases and not lump them under the meaningless term of pre-eclampsia

I heartily agree with Professor Fekete (March 22) when he stresses dysharmonious function of the various hormones rather than the overactivity of one as the cause of "pre-eclampsia", and that hypertension and H+P occur not infrequently for the first time during the puerperium [1]

I have postulated that the "pregnancy toxæmias" are due to malnutrition and mechanical factors The malnutrition may be due to an inadequate or unbalanced maternal diet (but not to deficiency of vitamin B_1), or to an inadequate blood-supply to the placenta This latter inadequacy may be due to local or generalised arterial spasm or to hypoplasia of the arterial tree, and is for the most part associated with maternal defects which preceded the pregnancy So far as I can see this hypothesis alone explains the geographical distribution of eclampsia, the variation in its incidence caused by war, and the fact that whereas the incidence of hypertension during pregnancy is unaffected by antenatal care, that of H+P and toxæmic accidental hæmorrhage can be greatly reduced and eclampsia can be eliminated

Finally may I be allowed to make one observation on Professor Browne's delightful letter concerning postmaturity (March 1)? The importance of this problem cannot be gauged by studying hospital reports, for its significance may vary from country to country and from city to city Who would have believed it possible that the incidence of anencephalus in "Belfast and Dublin was approximately three times greater than in Birmingham, ten times greater than in Malmo and Lund, and fifty times greater than in Lyons"? [2] During 1947 we induced labour because of postmaturity in 334 patients and all the mothers and all the babies went home alive, the credit belonging to the registrars and nursing staff

Bradford G W THEOBALD

SIR,—Both Professor Browne (Jan 18) and Professor Fekete (March 22) appear to accept the view that there is hyperfunction of the adrenal cortex in normal pregnancy, although Professor Fekete does not believe that this organ plays a major part in the ætiology of pre-eclampsia While the raised levels of plasma-cortisol during gestation [3] and some of the clinical features suggest that in normal pregnancy the adrenal glands are hyperfunctional, recent evidence does not support this view

Migeon [4] and his colleagues, by demonstrating that the half-life in the plasma of administered radioactive cortisol is prolonged in normal pregnant women, have shown that the rise in plasma-cortisol may be due to delayed inactivation or utilisation In keeping with this hypothesis Appleby and Norymberski [5] have provided evidence that the excretion of 17-hydroxycorticosteroids in the urine of normal pregnant women does not increase greatly during gestation A study in this laboratory, as yet unpublished, of the excretion of the unconjugated cortisol and cortisone in the urine shows a similar moderate rise in pregnant women, although there was relatively no change in the conjugated steroids measured Moreover, little, if any, alteration in weight of the adrenal gland occurs during pregnancy in the human female, and the histological picture does not resemble that of prolonged stimulation by corticotrophin (A C T H) [6] Hyperfunction of the adrenal cortex is associated with excessive catabolism of the body proteins,[7] but in normal pregnancy with adequate nutrition considerable retention of nitrogen, potassium, and phosphate occurs and there is also evidence of an increase in the maternal cell mass [8-10] Thus isotopic, morphological, metabolic, and hormone-excretion studies provide no evidence to support the view that pregnancy is associated with hypersecretion of the important glucocorticoid, cortisol

Though it is possible that the inactivation or utilisation of aldosterone may alter in a way similar to cortisol there is as yet no evidence for this Our view that the increased amounts of aldosterone-conjugate present in the urine of pregnant women [11 12] is a reflection of a homeostatic response to an increased need for sodium conservation by the kidneys [13] is based on the assumption that the rate of aldosterone excretion in the urine is *indeed* related to its production by the adrenal cortex The low values obtained in pre-eclamptic toxæmia may be due to an inhibitory effect of the enlarged extracellular volume

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C H GRAY
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[1] Theobald G W *Lancet* 1932, ii, 1380 The Pregnancy Toxæmias, p 164 London, 1955

2 *Brit med J* March 22, 1958, p 695
3 Gemzell, C A *J clin Endocrin* 1953, 13, 898
4 Migeon, C J, Sandberg, A A, Decker H A, Smith, D F, Paul A C, Samuels, L T *ibid* 1956 16 1137
5 Appleby, J I, Norymberski J K *J Endocrin* 1957, 15, 310
6 Whiteley, H J, Stoner, H B *ibid* 1957, 14, 325
7 Albright F *Harvey Lect* 1942–3, 38, 123
8 Wilson, K M *Johns Hopk Hosp Bull* 1916, 27, 121
9 Hummel, F C, Sternberger, H R, Hunscher, H A, Macy, I G *J Nutr* 1936, 11, 235
10 Seitchik, J Alper, C *Amer J Obstet Gynec* 1956, 71, 1165
11 Venning E H, Primrose, T, Caligaris, L C S, Dyrenfurth, I *J clin Endocrin* 1957, 17, 473
12 Martin, J D Mills, I H *Brit med J* 1956, ii, 571
13 Rinsler, M G, Rigby, B *ibid* 1957, ii, 966

breast In April, 1957, several secondaries in ileum were treated with local radiotherapy and radiation-induced menopause In May, 1957, she was put on methyltestosterone 50 mg and thyroid gr 2 daily She was very ill with persisting vomiting and dysphagia till August, 1957, when sudden improvement occurred which has been maintained The patient is now very fit and back to work Weight in September, 1957, 10 stone 9 lb , in March, 1958, 12 stone 3 lb (!) while still on thyroid gr 2 and methyltestosterone 50 mg daily

Nottingham G Fielding

POSTOPERATIVE HYPOTENSION

Sir,—It surprises me that in 1958 you can say, in your annotation of March 15, that occasionally the cause of postoperative hypotension "is less obvious, as when oligæmia from unobserved blood-loss during operation leads to" it Unobserved! "Unheeded" would often be apter Let the anæsthetist argue with the surgeon during the operation about blood-loss and the desirability of quantitative replacement He usually, for better or for worse, concludes his responsibility shortly after the patient returns to the ward Then what may the surgical resident find waiting for him there?

Perhaps not only the "unobserved" 1500 ml of de Wardener et al ,[1] but, far more often unheeded, the prospect of a postoperative ooze of another litre or so occurring during the next 24 or 48 hours

Donating blood, I may lose 540 ml without turning a hair or constricting a skin vessel But then I haven't had an anæsthetic nor have I a wound to heal nor an infection to prevent And not a drop more will leave the circulation This often-quoted analogy is an irrelevant one

Letheringsett,
Norfolk. J N Cozens-Hardy

SMOKING AND RESTLESS YOUNG MEN

Sir,—The far-fetched hypothesis that tobacco-smoking and lung cancer have partly a common cause in a constitutional factor is, as your annotation of March 29 points out, very difficult to accept Even if it was acceptable it would hardly affect the case against tobacco, but it and similar theories will continue to fog the issue so long as tobacco has defenders or until the cancer-smoking causal relationship is completely elucidated, or its existence proved beyond all possible argument by controlled experiment

In your same issue (p 657) Dr Doll and his colleagues report a controlled experiment proving that smoking, continued during treatment, delays the healing of peptic ulcers Surely experiments such as this should also be made to discover more completely many of the other relationships of smoking to health? In many cases the facts are in doubt, and as far as cancer is concerned the last refuge of the obscurantist and wishful thinker would be destroyed The national resources available for anti-tobacco education are necessarily limited, and there is therefore a sound ethical case for constituting some of the first beneficiaries of it into an experimental group This has been done with poliomyelitis vaccine and fluoridated water-supplies, in the latter case more to demonstrate the facts than to discover them Schools and places of employment, as well as residential areas, might determine the grouping, and a scientific study of motivation and of different techniques of education and persuasion might also be included in the experiment

London, S W 10 R B D Stocker

MORTALITY OF SEVERE HEAD INJURIES

Sir,—After reading the excellent article by Mr Maciver and his colleagues (Feb 22), I wish to draw attention to the dramatic response in patients with head injury to thiopentone cautiously given intravenously in dilute solution, after the initial shock has been combated[1] The patients improved greatly, in that hyperpyrexia and high blood-pressure were lowered and bronchial secretion and restlessness reduced

We feel that thiopentone has some coordinating action on the reticular activating system[2] and that the "lytic cocktail" is in some ways dangerous, by increasing the effects of anoxæmia in the tissues, particularly the brain

Amsterdam. T Wilhelmus

SEPARATION OF MOTHER AND CHILD

Sir,—I have long supported the "separation anxiety" thesis, even before it was as fashionable as it has become today It figured very largely in the psychopathology developed and taught by Hadfield,[3] Suttie,[4] and others at the pre-war Tavistock Clinic Their views were amply confirmed in the child-guidance clinic, and one had no need to devise any special theory, or elaborate statistical evidence, to appreciate to its full extent the protective role of the mother in creating the requisite emotional security for the young child's upbringing It was a natural corollary to pay attention therefore to anything disturbing the mother-child relationship, whether from within or from without

Separation of a child from its mother-figure undoubtedly *can* be traumatic, and an estrangement even more so But this is a far cry from Dr Bowlby's thesis (March 1) which has laid so much at the door of the *physical* separation of mother and child Dr Howells (March 29) rightly maintains that "Separation and privation are not synonymous terms", separation can and does occur without privation, as well as vice versa

Statistical investigations on the subject are valuable in their way, but, to repeat a platitude, one must ask for caution in their interpretation I still think that our prime need is for more and careful clinical studies of the *total* situation where mother and child have to be separated With regard to hospital separations it is many years now since I asked[5] for further inquiry into what kind of children are adversely affected? how far? and in what way?—including of course a study of the reverse process of recovery in those overcoming the "trauma" of separation

Exaggeration has provoked the inevitable reaction, and I was amused to read of Margaret Mead's outburst[6] calling the thesis "a new and subtle form of antifeminism in which men —under the guise of exalting the importance of maternity—are tying women more tightly to their children than has been thought necessary since the invention of bottle feeding and baby carriages"

One hazard which it seems we have not escaped is the premature dissemination to the public at large of opinions which as yet are not fully authenticated A recent pamphlet put out by the National Association for Mental Health[7] presents the problem moderately enough, but is sufficiently loaded to cause undue anxiety to already anxious mothers This April sees the centenary of the birth of Truby King, who in his turn tried to impose a rigid pattern of infant-feeding on the mothers of his day, which is now generally regarded as outmoded

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[1] *Clin Sci* 1953, 12, 175

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[1] Blitz, J *Ned Tydschr Geneesk* 1958, 102, 345
[2] French, J D , Verzeano, M D , Magoun, H W *Arch. Neurol Psychiat , Chicago*, 1953, 69, 505
[3] Hadfield, J A Psychology and Mental Health London, 1950
[4] Suttie, I D Origins of Love and Hate London, 1935
[5] Edelston, H *Genet Psychol Monog* 1943, 28, 3
[6] Quoted by Carstairs, G M *J ment Sci* 1958, 104 70
[7] Bowlby, J Can I Leave my Baby ? 1958

Perhaps the crux of the matter lies in the discovery of the "great heterogeneity of personality organisation" which defies classification and asks for a patient and sympathetic understanding of each situation in its own right Finally I would call attention to the serious danger of using pathological reactions as a basis on which to erect standards of behaviour for normal people, in so doing are we not putting a premium on the element of adventure in really healthy living?

Bradford H EDELSTON

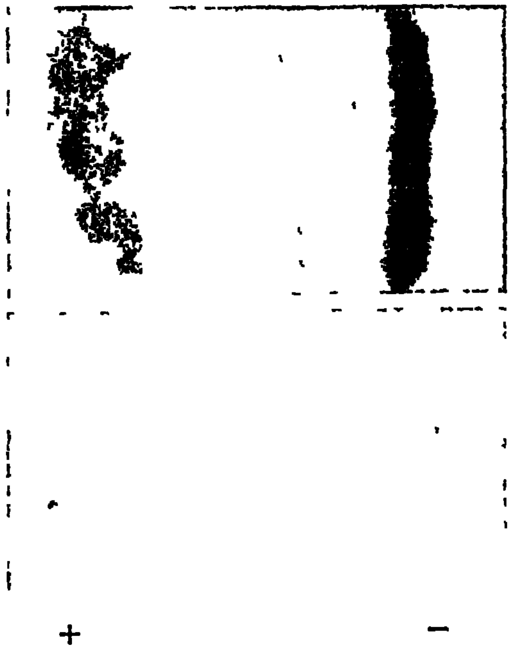
UNUSUAL URINE PROTEIN IN MYELOMATOSIS

SIR,—The new technique of electron microscopy has helped towards the understanding of the physical principle of glomerular ultrafiltration Glomerular capillary walls of kidney are structurally specialised, with channels and spaces somewhat similar to those of collodion membranes prepared for use as an ultrafilter [1]

In our experiments, by ultrafiltration of normal and pathological sera through collodion membranes of suitable porosity, ultrafiltrates were obtained, the patterns of which corresponded to the patterns of pathological urine proteins [2,3] The concentrated ultrafiltrates of sera were investigated by paper electrophoresis

We also examined serum ultrafiltrates from patients with myelomatosis and macroglobulinæmia In each case, electrophoresis revealed an additional electrophoretically homogeneous serum-protein fraction Even here we were able to find a similarity between natural and artificial ultrafiltrates

In one patient with myelomatosis we saw an interesting phenomenon [4] The simple paraproteinæmic serum fraction split, after filtration through membrane of a known porosity, into two clearly separated components, during analysis of ultrafiltrate proteins by paper electrophoresis (see figure) The splitting of this fraction we took to be a result of a change in the electrical charge on colloidal molecules caused by mutual action of membrane pores and protein particles during the filtration process



Above: Electrophoretic protein pattern of serum from a patient with myelomatosis shows a single γ-globulin fraction; below: Electrophoretic pattern of concentrated ultrafiltrate of the same serum shows two γ-globulin components Both electrophoretograms were done under the same conditions

As the discussion in your correspondence columns shows,[5–7] a similar phenomenon was sometimes seen in the sieving effect of the biological glomerular membrane on the blood-proteins passing into the urine In this connection the idea of an analogy between the glomerular membrane and the artificial collodion membrane may be useful

Department of Experimental Pathology,
Masaryk University, Brno,
Czechoslovakia D WIEDERMANN

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1 Hall, V *Amer Heart J* 1957, 54, 1
2 Wiedermann, D, Šmarda, J *Schweiz med Wschr* 1956, 86, 930
3 Wiedermann, D, Šmarda, J *Physiol Bohemoslov* 1957, 6, 232
4 Wiedermann, D, Šmarda, J, Wiedermann, B *Z exp Med* 1957, 129, 286

INSTITUTIONAL CARE OF THE MENTALLY ILL

SIR,—In the article by Dr Garratt and his colleagues (March 29) there is one point which I do not think should go unchallenged Under the heading of "supervision" they say that there "could be no reasonable objection" to the employment of general-trained nurses to attend to some of the less disturbed psychiatric patients

When this survey was being made, the psychiatrists were asked to designate patients who needed no (or minimal) psychiatric nursing supervision But this does not mean that general-trained nurses would be acceptable

What such patients require emotionally is the kind of competent mothering which is a fairly common skill in married women of mature age (our untrained part-time nurses tend to have it in good measure) Unfortunately, the pattern of general nursing training, with its emphasis on purely technical abilities, is still such as to spoil rather than to foster this kind of skill in human relationships Nurses in general hospitals tend to be far more upset by the presence of a "psychiatric patient" than is the community at large

I would therefore recommend that the psychiatric patient with minimal disability should be cared for either by untrained nurses (under psychiatric supervision), or, if the general-trained nurse is the only possibility, she should have been away from general nursing for long enough to have recovered from it—say, at least five years

Hollymoor Hospital,
Northfield, Birmingham J R MATHERS

PSYCHOSIS AND TREMOR DUE TO MECAMYLAMINE

SIR,—We have a gentleman in the ward at the moment with what we believe to be the mecamylamine toxic syndrome described by Dr Harington and Dr Kincaid-Smith (March 8)

He came to us seven months ago as an emergency with an episode of hypertensive encephalopathy, and while in the ward had a minor subarachnoid hæmorrhage His blood-pressure was 260 + /110 mm Hg and blood-urea 27 mg per 100 ml His recovery from these complications was uneventful but we found it necessary to keep him on a dose of 30 mg of mecamylamine six-hourly and he was later discharged on this dosage At this time his blood-pressure was 180/120 and his blood-urea 25 mg per 100 ml

He was followed up at regular intervals and made good progress In February he was normotensive and had a blood-urea of 45 mg per 100 ml

Two weeks ago he was readmitted because of a generalised coarse tremor and difficulty with his speech There was also some pruritus of the legs The tremor affected his whole body and was present at rest so that his bed shook It was accentuated by voluntary movement and so much so that he was unable to

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5 Cummings, A J *Lancet*, 1957, ii, 598
6 Gobert-Jones, J A *ibid* p 1068
7 Owen, J A *ibid* p 1286

drink a cup of tea There were no hallucinations or other mental changes, however, and no localising signs in the central nervous system His blood-pressure was now 240/130 and blood-urea 66 mg per 100 ml

The mecamylamine has been withdrawn since then and there has been a marked improvement in his symptoms His tremor is such that he can now write legibly and speech is no longer slurred and jerky His blood-pressure remains at 240/140 and his blood-urea is 53 mg per 100 ml

This case seems to fit in with the syndrome described by Dr Harington and Dr Kincaid-Smith Three features we feel are of special interest (1) the very high dosage of mecamylamine, (2) the satisfactory response to withdrawal of the drug, and (3) the fact that only two blood-urea estimations during the whole illness have been slightly above the upper limit of normal In view of these facts we are not convinced that any part of his symptom complex was due to uræmia

The General Hospital,
Chester-le-Street,
Co Durham

JOHN A LENNOX

THE FUTURE OF THE PUBLIC HEALTH LABORATORY SERVICE

SIR,—Your comment (April 5, p 730) that the separation of the Public Health Laboratory Service from the hospital laboratory service is in places too wide deserves study

The field of the P H L S is bacteriology applied to preventive medicine, but between this and other branches of medical bacteriology it is no longer easy to draw a sharp line Is the throat swab taken from the child suspected of having scarlet fever to confirm the diagnosis or for the benefit of his contacts or of the community? The virtual disappearance of such diseases as typhoid fever, the radical changes in the management of tuberculosis, and the improved prognosis in, for example, puerperal infections, have all helped to confuse a distinction which was much clearer twenty years ago The isolation hospital and the tuberculosis clinic, both former preserves of the P H L S, are now administered by the regional hospital board Almost everywhere the general practitioner can send his specimens to the hospital laboratory Except for water and foodstuffs the number of bacteriological specimens provided by the health departments of local authorities seems to be less than it was The P H L S has done excellent work in diagnostic virology in many places, but it is only a matter of time before the hospital laboratories take advantage of the experience obtained in this field

The P.H.L S has had advantages in its generous scales of technical staff and equipment It has provided good opportunities for work with the minimum of interference and red tape It has developed an admirable ésprit-de-corps It has almost certainly done much to raise the standards of medical bacteriology in this country It has produced much original work of high quality and in particular has demonstrated the value of large-scale cooperative investigations Nevertheless it is now open to argument whether we can afford to maintain a duplicated bacteriological service except in those towns large enough to provide sufficient public-health bacteriology to keep one laboratory busy In the smaller towns public-health bacteriology seldom provides more than a part of the work of the P H L S laboratories which fill in their time with the leavings of the hospital laboratories and even compete with them for the custom of the general practitioners

It is not a question of abolishing the P H L S but of examining its structure and working to see how best it may take its share of the medical bacteriology without lowering its standards or forgetting its traditions The time is past when laboratories could be established and conducted on an empirical basis The planning of hospital services has advanced to the point where we can make a reasonable guess about the needs of the next twenty-five years The P H L S laboratories should be fitted into these plans as soon as possible, not by local and informal agreement but in accordance with some integrated design

A PROVINCIAL PATHOLOGIST

BUDGERIGARS AND POLIOMYELITIS

SIR,—Haunted by the budgerigar carrying polio virus, we have examined those sera of household pets still in our deepfreeze (dating from 1951 till March, 1958) for neutralising antibodies against all 3 types of poliovirus The sera were tested with a modified colour test in plastic plates in a dilution of 1 in 10 37 budgerigars, 4 parrots, 2 canaries, 52 pigeons, 2 cats, and 5 dogs had no neutralising antibodies in their serum, but 1 dog had antibodies against polio type-I in his serum

It seems that polio infection in household pets, at least in Holland, might be a rare event

Virus Laboratory,
Laboratorium voor de Gezondheidsleer,
University of Amsterdam

F DEKKING

THE BURNING-FEET SYNDROME

SIR,—You have commented (March 8) on Bibile et al 's report[1] that they had failed to observe any significant difference in the proportion of cures obtained in the burning-feet syndrome between pantothenol (alcohol derivative of pantothenic acid) and a placebo Of 38 patients they treated with pantothenol orally or parenterally, 22 were either cured or improved On the other hand, out of 18 patients treated with a placebo, 11 were either cured or improved Dr Bibile and his coworkers have rightly concluded that pantothenic-acid deficiency was not the cause of burning feet *in the patients investigated by them*

On the other hand, the fact that pantothenic-acid deficiency may produce burning feet is suggested by a number of observations

In burning feet associated with signs of vitamin-B-complex deficiency, benefit has followed on administration of pantothenic acid[2] Defective acetylation of para-aminobenzoic acid, indicating pantothenic-acid deficiency, has also been reported in these cases[3] The work of Bean et al[4] has provided further evidence of the role of pantothenic-acid deficiency in burning feet By administering a pantothenic-acid antagonist to human volunteers, these workers were able to produce paræsthesia of the limbs, burning feet, and hyperactive reflexes When pantothenic acid was given, the paræsthesiæ, including burning feet, disappeared completely

In the light of this evidence, the question arises whether the burning feet investigated by Bibile et al were in fact of nutritional origin In this connection their observation that they obtained improvement in 11 out of 18 cases treated with a placebo alone would seem significant. Your annotation does not draw attention to this important point

The duration of the disease before treatment in their cases was reported to vary from as long as eighteen to forty-four

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[1] Bibile S W Lionel, N D W, Dunuwille, R., Perera, G *Brit J Nutr* 1957, 11, 437
[2] Gopalan C *Indian med Gaz* 1946 81, 22.
[3] Sarma, P S, Menon, P S, Venkatacholam, P S *Curr Sci* 1949, 18, 367
[4] Bean, W B, Hodges, R E., Daum, K *J clin Invest* 1955, 34, 1073

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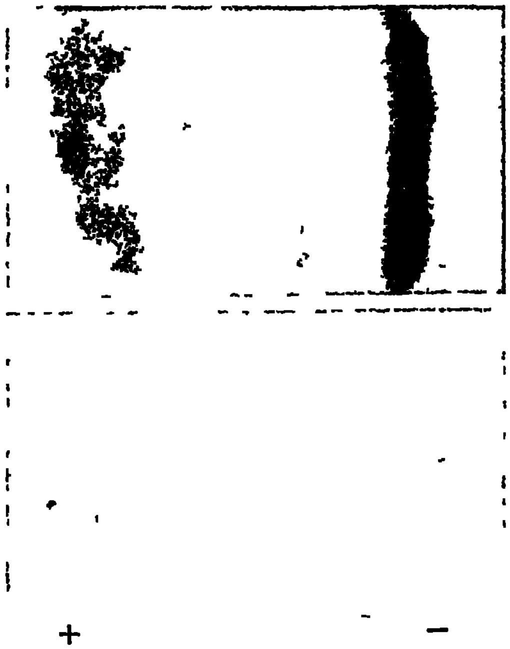

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7 Owen, J A *ibid* p 1286

drink a cup of tea There were no hallucinations or other mental changes, however, and no localising signs in the central nervous system His blood-pressure was now 240 130 and blood-urea 66 mg per 100 ml

The mecamylamine has been withdrawn since then and there has been a marked improvement in his symptoms His tremor is such that he can now write legibly and speech is no longer slurred and jerky His blood-pressure remains at 240 140 and his blood-urea is 53 mg per 100 ml

This case seems to fit in with the syndrome described by Dr Harington and Dr Kincaid-Smith Three features we feel are of special interest (1) the very high dosage of mecamylamine, (2) the satisfactory response to withdrawal of the drug, and (3) the fact that only two blood-urea estimations during the whole illness have been slightly above the upper limit of normal. In view of these facts we are not convinced that any part of his symptom complex was due to uræmia

The General Hospital,
Chester-le-Street,
Co Durham

JOHN A LENNOX

THE FUTURE OF THE PUBLIC HEALTH LABORATORY SERVICE

SIR,—Your comment (April 5, p 730) that the separation of the Public Health Laboratory Service from the hospital laboratory service is in places too wide deserves study

The field of the P H L S is bacteriology applied to preventive medicine, but between this and other branches of medical bacteriology it is no longer easy to draw a sharp line Is the throat swab taken from the child suspected of having scarlet fever to confirm the diagnosis or for the benefit of his contacts or of the community? The virtual disappearance of such diseases as typhoid fever, the radical changes in the management of tuberculosis, and the improved prognosis in, for example, puerperal infections, have all helped to confuse a distinction which was much clearer twenty years ago The isolation hospital and the tuberculosis clinic, both former preserves of the P H L S, are now administered by the regional hospital board Almost everywhere the general practitioner can send his specimens to the hospital laboratory Except for water and foodstuffs the number of bacteriological specimens provided by the health departments of local authorities seems to be less than it was The P H L S has done excellent work in diagnostic virology in many places, but it is only a matter of time before the hospital laboratories take advantage of the experience obtained in this field

The P.H.L S has had advantages in its generous scales of technical staff and equipment. It has provided good opportunities for work with the minimum of interference and red tape It has developed an admirable esprit-de-corps It has almost certainly done much to raise the standards of medical bacteriology in this country It has produced much original work of high quality and in particular has demonstrated the value of large-scale cooperative investigations Nevertheless it is now open to argument whether we can afford to maintain a duplicated bacteriological service except in those towns large enough to provide sufficient public-health bacteriology to keep one laboratory busy In the smaller towns public-health bacteriology seldom provides more than a part of the work of the P.H.L S laboratories which fill in their time with the leavings of the hospital laboratories and even compete with them for the custom of the general practitioners

It is not a question of abolishing the P H L S but of examining its structure and working to see how best it may take its share of the medical bacteriology without lowering its standards or forgetting its traditions The time is past when laboratories could be established and conducted on an empirical basis The planning of hospital services has advanced to the point where we can make a reasonable guess about the needs of the next twenty-five years The P.H L S laboratories should be fitted into these plans as soon as possible, not by local and informal agreement but in accordance with some integrated design

A PROVINCIAL PATHOLOGIST

BUDGERIGARS AND POLIOMYELITIS

SIR,—Haunted by the budgerigar carrying polio virus, we have examined those sera of household pets still in our deepfreeze (dating from 1951 till March, 1958) for neutralising antibodies against all 3 types of poliovirus The sera were tested with a modified colour test in plastic plates in a dilution of 1 in 10 37 budgerigars, 4 parrots, 2 canaries, 52 pigeons, 2 cats, and 5 dogs had no neutralising antibodies in their serum, but 1 dog had antibodies against polio type-I in his serum

It seems that polio infection in household pets, at least in Holland, might be a rare event

Virus Laboratory,
Laboratorium voor de Gezondheidsleer,
University of Amsterdam

F DEKKING

THE BURNING-FEET SYNDROME

SIR,—You have commented (March 8) on Bibile et al's report[1] that they had failed to observe any significant difference in the proportion of cures obtained in the burning-feet syndrome between pantothenol (alcohol derivative of pantothenic acid) and a placebo Of 38 patients they treated with pantothenol orally or parenterally, 22 were either cured or improved On the other hand, out of 18 patients treated with a placebo, 11 were either cured or improved Dr Bibile and his coworkers have rightly concluded that pantothenic-acid deficiency was not the cause of burning feet *in the patients investigated by them*

On the other hand, the fact that pantothenic-acid deficiency may produce burning feet is suggested by a number of observations

In burning feet associated with signs of vitamin-B-complex deficiency, benefit has followed on administration of pantothenic acid[2] Defective acetylation of para-aminobenzoic acid, indicating pantothenic-acid deficiency, has also been reported in these cases[3] The work of Bean et al[4] has provided further evidence of the role of pantothenic-acid deficiency in burning feet By administering a pantothenic-acid antagonist to human volunteers, these workers were able to produce paræsthesia of the limbs, burning feet, and hyperactive reflexes When pantothenic acid was given, the paræsthesiæ, including burning feet, disappeared completely

In the light of this evidence, the question arises whether the burning feet investigated by Bibile et al were in fact of nutritional origin In this connection their observation that they obtained improvement in 11 out of 18 cases treated with a placebo alone would seem significant. Your annotation does not draw attention to this important point.

The duration of the disease before treatment in their cases was reported to vary from as long as eighteen to forty-four months The fact that they obtained such gratifying results with placebo alone (cure or improvement in 11 out of 18 cases) seems to throw doubt on their nutritional origin It seems very unlikely that a syndrome of chronic malnutrition of several months' duration could be so successfully treated with a placebo in four weeks In the selection of their cases Bibile et al were apparently guided solely by the presence of paræsthesia of the limbs Their table listing the clinical features does not mention such signs of vitamin-B-complex deficiency as angular stomatitis, glossitis, scrotal dermatitis, &c On the other hand, all the cases of burning-feet syndrome that benefited from pantothenic-acid [3] had shown advanced signs of vitamin-B-complex deficiency In these cases hyperhidrosis was much more evident and actual aching in the limbs much less prominent than in the series of Bibile et al Evidently the two series were different not only ætiologically but also clinically

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[1] Bibile, S W Lionel N D W, Dunuwille, R., Perera G *Brit J Nutr* 1957, 11, 437

[2] Gopalan, C *Indian med Gaz* 1946, 81, 22.

[3] Sarma, P S Menon, P S, Venkitachalam, P S *Curr Sci* 1949, 18, 367

[4] Bean, W B, Hodges, R. E., Daum, K. *J clin Invest* 1955, 34 1073

Paræsthesia of the feet may of course have many causes, and it is obviously unjustifiable to attribute all burning feet to malnutrition In our own clinic in Coonoor, we see some burning feet unassociated with clinical evidence of malnutrition, in which naturally no nutritional therapy, including pantothenic acid, yields significant benefit Moreover, acetylation of *p*-aminobenzoic acid has been found normal in these cases It is possible that some of them are of functional origin, and may improve with suggestion and administration of placebo

Nutrition Research Laboratories,
Indian Council of Medical Research,
Coonoor, Nilgiris, South India
C GOPALAN

TOTAL EXCHANGEABLE SODIUM IN HÆMORRHAGIC SHOCK

SIR,—Plasma volume is diminished in most cases of hæmorrhagic and traumatic shock There are, however, few data on the behaviour of the extracellular space in shock [1] We have investigated the question by continuous determination of ^{24}Na space (indicating total exchangeable sodium) in dogs in the normal state, in posthæmorrhagic hypotension, and after reinfusion of the blood

The dogs were given about 20 μc of ^{24}Na intravenously, and the ^{24}Na space was calculated after 3 hours by the usual technique Bleeding and reinfusion were carried out by the standard technique of Wiggers [2] (90 min at 50–60 mm Hg, 45 min at 30–40 mm Hg) The ^{24}Na space was repeatedly determined in the hypotensive period and after reinfusion for about 6 hours

Six dogs died in shock within 2–6 hours of reinfusion Six survived the 6-hour period In all the dogs which succumbed to shock the ^{24}Na space showed a progressive increase up to 25% of the control values In the survivors, there was no change in sodium space The plasma-sodium level remained unchanged in all experiments

As we have previously observed in nephrectomised dogs that the inulin space does not change in hæmorrhagic shock, the increase of the ^{24}Na space—with the plasma-sodium levels unchanged—can hardly be due to the increase of extracellular sodium Accepting inulin space as a measure of extracellular space, the increase in exchangeable sodium must be the consequence of the increment of intracellular sodium That part of the intracellular sodium which is not exchangeable under normal conditions probably becomes exchangeable in shock

A detailed account of our data will be published elsewhere

L HÁRSING
J NAGY
G KÖVÉR
E DUBECZ
Physiological Institute and
Institute for Medical Physics,
Medical University, Budapest

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[1] Rosenthal, S M, Millican R C *Pharmacol Rev* 1954, 6, 489
[2] Wiggers, C J Physiology of Shock New York, 1950

THE DOCTOR'S ATTITUDE TO HIS PATIENT

SIR,—Like Dr Ryle (March 1) I have been waiting for a gun of some calibre to sink Dr Clyne (Feb 1) and am only tempted to interfere by the absence of any such "official" armament and from the presence now of a second sail, Dr Pasmore (March 8)

I read Dr Clyne once and thought it was queer that the article had arrived there at all, then I read it again with more sympathy for his difficulties, and I have read it a third time but still cannot let him off I kept thinking he should look at Luke Fildes' picture, he would find there another doctor who could not say what was wrong with his small patient but at least was observing the clinical course Admittedly his vigil is hypocritical in being valueless to the child, but he may have learnt something himself I am sure that is not what Fildes wanted to express, he was after the love and devotion, but more factually that doctor's only hope was to know better next time I am using this example to suggest that Dr Clyne has been unfortunate in trying to hang his analytic weeds on an unsuitable peg, because they fall to a heap as certainly as it is obvious that when he received that call that morning he could not write his paper at the same time as know what was the matter with the child

Seen this way it becomes plain that his guilt-hostility discussion could never have arisen if his clinical wit and decision had not been clouded by his eagerness to pay attention to other things than the child's disease, you remember that Fildes kept the parents dark in the background, and Dr Clynes tacitly demonstrates the only person who took an objective view of the case, the patient's father, who is dubbed for his strength a weak character The document is therefore anti-clinical, Dr Ryle thinks it anti-scientific as well, but that does not concern me so much Anti-clinical it is, and the range is the same for the second sail, Dr Pasmore

You have offered him broadside by publishing his fuller article in the same issue (March 8) as his letter His basal error is the same as that of Colin Wilson, who wrote a most attractive book about a bunch of most attractive lunatics Unfortunately he tried to draw a social lesson from them and foundered on the fallacy There are lessons to draw from such people, either their lunacy with or without the charm, or the charm without the lunacy, none of these three is a social lesson, meaning a moral or ethic applicable to other people *Modern medicine is in the* same quandary towards the recently unearthed mass of minor neurotics, who always were present of course but did not go to doctors There is no social lesson to learn from these people and it is a fallacy to think there is, and if the profession swallows them whole it can only become neurotic itself, if it is wise it will take what it wants off this world (after all, who wishes to be unemotional?), and it will leave the rest either to recover, as many do, remain neurotic, as many do, or become psychoneurotic, as very few do It is however anti-clinical to move the couch too near the confessional and it brings queer reasoning Dr Pasmore betrays great pride and complacency when he unearths the fact that his "intelligent secretary" was not so much worried by the poliomyelitis of her cousin as the loss of her fiancé But what would have been the doctor's illumination if these trophies had been dug up in the other order, as they could have been?

This sort of inquiry is specious but not specific, all it says is that this patient is the sort of patient who is likely to make a muddle of a romance, fair enough, is likely to be greatly upset when it crumbles, fair enough, can also be upset by the poliomyelitis of her cousin, fair enough, is emotionally insecure, fair enough, but is quite capable of either a happy marriage or a useful life, or both, fair enough The emotional history should not have any direct influence on the doctor's clinical opinion, in this case, the reason why her legs were weak This reason may be functional as we all know, but the clinician reaches that opinion without the emotional history, and can give just as good advice and can get just as good a result without ever hearing it

SCANNER

SIR,—I thought Dr Ryle's letters were very refreshing, and Dr Pasmore's perhaps a shade irascible from one adept at suppressing parts of his personality I also confess to "outmoded obscurantism" and delude myself into thinking that I can "achieve a reasonable understanding without undergoing personality change" Nor do I see anything unsound in our giving what active, positive advice we truthfully think is most helpful, according to our own principles, biases, morals, religions, and backgrounds We are, doctors and patients, all irrational human beings in it together and, unfortunately, analysis or personality change, whilst making a doctor more aware of his own emotional characteristics (why "disabilities"?), may not make him wiser or kinder, warmer-natured or more intelligent, or less of a crank than he might otherwise have been

The negative, passive attitude (What do you think I should do doctor? Well, what do *you* think?) mistakenly assumes most patients to be unable, inwardly or outwardly, to criticise us, or our advice, to amend or to reject it, or indeed to have any sensible view of our fallibilities at all Conversely, to assume that analysis or personality change produces in the doctor a mind so aloof from its own peculiarities that it can be used on fellow humans as a "scientific instrument" betrays a humourless superiority of attitude, a conviction of post-analytical rightness, that some of us find the least acceptable facet of the psychiatric approach

London, S W 7 **BENJAMIN LEE**

SIR,—Dr Pasmore (March 29) has restated his case with vehemence but no new evidence

Can he cite references for his bald claim that "scientific inquiry has shown that the psychoanalyst cannot practise his specialty without undergoing an analysis himself, and recent research suggests that the general practitioner cannot attempt similar work in a limited field without undergoing some modified analysis or personality change"? Dr Pasmore may be convinced that psychoanalytical theory is true but he has no right to close his eyes to the fact that non-analysed psychiatrists and G P s who have never been to a Tavistock seminar are treating neuroses

One of the reasons for my original letter criticising Dr Clyne's article was to question its apparent assumption that the tenets of psychoanalysis were proven A widely held opinion does not constitute a scientific fact, and psychoanalysis remains scientifically dubious because it is full of untestable hypotheses and hence prone to repeated revision, schism, and inconsistencies, because it pays so little heed to allied sciences and because its claim to exclusive therapeutic efficacy remains unproved [1,2] Workers holding non-analytical views have reported results as good or better and usually quicker—e g, Phillips [3] and Wolpe [4]—and are able to explain and accept the effects of analysis, a tolerance not often reciprocated T A Ross, whose books [5,6] did so much to introduce psychotherapy into general practice, was much concerned lest the analysts, with their claim to exclusive truth, should gain control of the teaching of the neuroses, his warning [7] deserves re-reading today

London, N W 5 **ANTHONY RYLE**

MITRAL VALVOTOMY AND PREGNANCY

SIR,—That mitral valvotomy is valuable is established If, however, valvotomy is to be allotted its proper place in the management of the pregnant woman with mitral stenosis, it should be compared only with the best method of treatment hitherto available—namely, strict medical supervision allied to conservative obstetrics [8,9] Since therapeutic abortion is not only valueless but positively dangerous, it is unfortunate that Dr Wade and his colleagues (March 15) should join Das and Chesterman [10] in confusing this important issue by recommending valvotomy as a substitute for termination

In our recent series of 289 cases of rheumatic heart-disease complicated by pregnancy,[9] in which no therapeutic abortion was performed, 1 mother failed to survive the puerperium and 8% of all conceptions failed to survive the neonatal period Our conclusion that therapeutic abortion is of no value has been confirmed by Gorenberg [11,12] On the other hand, Jones [13] showed that abortion is dangerous he recorded 2 maternal deaths due to therapeutic abortion in a series of 352 heart cases In this series the fœtal wastage directly due to termination was 6 4% Fitzgerald et al [14] corroborate this in reporting 3 maternal deaths in 450 cases All 3 deaths followed termination

Valvotomy was performed during pregnancy in 3 of our 289 cases In each case mother and baby survived Dr Wade and his colleagues performed the operation on 12 pregnant women, but do not state the total number of cases from which these were selected Of the 12, 1 mother died, 1 developed a hemiplegia, 1 had a rheumatic recrudescence with associated heart-failure and 1 had pulmonary œdema post partum 2 babies were lost

We submit that this evidence does not invalidate our conclusion that, when a patient with mitral stenosis responds favourably to medical treatment, operation should be deferred until after delivery [9]

M K O'DRISCOLL
Dublin **M I DRURY**

A BALANCED HOSPITAL COMMUNITY

SIR,—The ideas suggested by Professor McKeown (April 5) for a balanced hospital community are an admirable contribution to medical planning and development, but I wish that he had gone further still

His theme of centralising hospital buildings and administration to achieve a better and a wider service for the community can be applied with even more force to the National Health Service as a whole Just as the hospitals are at present dispersed and isolated, providing a limited service for selected groups of patients, so we have in the N H S a system whereby the three branches—hospitals, general practitioners, and public-health workers—are administered and organised by three separate and distinct

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[1] Denker, P C *N Y St med J* 1946, 46, 2164
[2] Eysenck, H J *J Consult Psychol* 1952, 16, 319
[3] Phillips, E L Psychotherapy a Modern Theory and Practice Prentice Hall New Jersey, 1956
[4] Wolpe J *Arch Neurol Psychiat* 1954, 72, 205
[5] Ross, T A The Common Neuroses London 1937
[6] Ross, T A Analytical Psychotherapy London, 1932
[7] Ross, T A *Edinb med J* 1935, 42, 445 *ibid* p 505
[8] Drury, M I, O Driscoll, M K, Hanratty, T D, Barry, A P *Brit med J* 1954, i, 70
[9] O'Driscoll, M K, Barry, A P, Drury, M I *ibid* 1957, ii, 1090
[10] Das, J B, Chesterman J T *ibid* 1958, i, 142
[11] Gorenberg, H, Chesley, L C *Obstet Gynec* 1953, 1, 15
[12] Gorenberg, H *Amer J Obstet Gynec* 1955, 69, 1253
[13] Jones, A M Heart Disease in Pregnancy London, 1951
[14] Fitzgerald, J E, Webster, A, Zummo, B P, Williams, P C *J Amer med Ass* 1951, 146, 910

bodies (the hospital committee, the executive council, and the local authority) each working away on its own with no more than a superficial contact with the other two All three are concerned with promotion of health and the prevention and treatment of disease Surely it would be rational to expect them to be planned, organised, and administered as single units, working together in cooperation for a common cause

I should like to suggest that we think of the future in terms of such a unified health service administered by a common body for each area These areas could conveniently be the present hospital group regions with the main hospital in each area serving as the focal point for all three medical branches The hospitals, general practitioners, and public-health workers would then be organised from a single source and this should add to a mutual appreciation of each other's problems and lead to a more cooperative spirit in a more efficient service

Beckenham,
Kent

JOHN FRY

Diary of the Week

APRIL 13 TO 19

Monday, 14th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W C 2
5 15 P M Mr Rodney Smith Pancreatitis
6 30 P M Mr Rainsford Mowlem The Treatment of Lymphœdema

Tuesday, 15th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
3 45 P M Dr R McP Livingston The Human Embryo—Development of Form (Arnott demonstration)
5 15 P M Sir Arthur Porritt Non-malignant Conditions of the Breast
6 30 P M Mr Ronald Furlong Osteo-arthritis of the Hip

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S W 1
5 P M Dr J St C Elkington Cerebral Vascular Disease in the light of Modern Techniques (First Lumleian lecture)

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W 1
5 30 P M Dr G F Swann Observations on Cerebral Arteriography

BIRMINGHAM MEDICAL INSTITUTE, Edgbaston, 15
8 P M *Psychiatry* Dr E S Stern Figuring it out—a statistical Approach to Psycho pathology and Prognosis

Wednesday, 16th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 15 P M Prof F A R Stammers Complications of Gastrectomy
6 30 P M Sir Harry Platt Congenital Dislocation of the Hip

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
5 P M *Comparative Medicine and Pathology* Dr Jack Colover, Mr R M Barlow, Prof C E Lumsden Recent Advances in Demyelinating Disease
8 15 P M *General Practice* Dr H G Barnes, Dr W F Hudson, Dr J D Huntley, Dr P M Higgins, Dr P A Walford, Dr Stephen Taylor Management of Practice

WEST LONDON MEDICO-CHIRURGICAL SOCIETY
8 30 P M (Royal Society of Arts John Adam Street, W C 2) Sir Gordon Gordon-Taylor On Tradition

OXFORD UNIVERSITY
5 P M (Radcliffe Infirmary) Dr John Kirklin The Surgical Treatment of Tetralogy of Fallot (Litchfield lecture)

Thursday, 17th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P M Mr A G Jessiman Hypophysectomy in the Treatment of Breast Cancer (Hunterian lecture)
6 15 P M Prof C A Wells Prostatic Obstruction

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S W 1
5 P M Dr Elkington Cerebral Vascular Disease in the Light of Modern Techniques (Last Lumleian lecture)

ROYAL SOCIETY OF MEDICINE
8 P M *Surgery* Dr J W Kirklin (Mayo Clinic) Repair of Atrial and Ventricular Septal Defects

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, S E 5
5 P M Dr A B Hollingshead Social Class and the Treatment of Mental Illness

Friday, 18th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 15 P M Mr R G Pulvertaft Reconstructive Surgery of the Hand
6 30 P M Mr Selwyn Taylor Radioactive Isotopes as an Adjunct to Surgery

ROYAL SOCIETY OF MEDICINE
5 P M *Epidemiology and Preventive Medicine* Dr R S F Schilling, Dr J C Gilson Mr S A Roach Epidemiology of Byssinosis
8 15 P M *Radiology* Dr E Duff Gray Radiological Aspects of Biliary Tract Disease (Presidential address)

INSTITUTE OF LARYNGOLOGY AND OTOLOGY 330, Gray's Inn Road W C 1
5 30 P M Mr J C Hogg Treatment of Frontal Sinusitis

Obituary

HECTOR CHARLES CAMERON

M A, M D Cantab, M A Glasg, F R C P

Dr Cameron, author of *The Nervous Child* and a pioneer of child guidance, died on April 1 in his 80th year The distinction of his mind and character, as well as of his work and writings, gave him much influence in pædiatrics, and he had a considerable share in its remarkable development

Son of Sir Hector Cameron, professor of clinical surgery at Glasgow, he went back to his native city when he left Clifton College, and took a Glasgow arts degree He then entered St John's College, Cambridge, as a foundation scholar in science, gained a first-class in the natural sciences tripos, and won a university scholarship at Guy's Hospital Qualifying in 1905, he was for a time demonstrator in physiology, and got the varied clinical experience obtainable in those days, combining at one time the appointments of medical registrar and tutor, assistant pathologist, physician to the nursing staff, and anæsthetist When he joined the Guy's honorary staff in 1911 he had been working as clinical assistant at the East London Hospital for Children and at the Evelina, and he decided to specialise in diseases of children Previously he had shown his literary bent as editor of the hospital gazette, and had already produced a succession of papers beginning with one on metastatic cerebral abscess, written with Mr W M Mollison, in *Guy's Hospital Reports* in 1907 His *Diet and Disease in Infancy* appeared in 1915 and the first edition of *The Nervous Child* in 1919 A master of the spoken as well as of the written word, he could tell a story supremely well, and his teaching, sometimes entertainingly acidulated, contained many of the sayings and anecdotes that stick in the mind

On bedwetting for instance, he said "Often the trouble with the enuretic child is not that he doesn't care but that he cares too much" And he told of a school where a housemaster wanted a boy expelled because he was a bedwetter "No", said the headmaster, "these are the boys who win scholarships"

Cameron was one of those doctors who have a really comprehensive approach to their patient's problem, considering not only the anatomical and biochemical disturbance but what is going on in his mind In consequence Guy's was the first teaching hospital to have, in 1931, a child-guidance department, and in the United States in the middle 1930s Cameron was by many regarded as the doyen or originator of the child psychiatry movement This was at a time when his teaching on these lines was largely ignored by his pædiatric colleagues

Outside his specialty, he did some regular life-assurance work which kept him in touch with the medicine of adults—though some felt sorry that he should have to divert any of his attention from the special subject to which he had so much to contribute Later, in years of retirement, he was able to make full use of his gifts as a historian

Such is the merest outline of a long and exceptionally fruitful life A clearer idea of his contributions to medicine, as thinker, clinician, and writer, is given by the following more personal tributes, the first from a senior, the second from a junior

Cameron belonged essentially to the older school of pædiatricians who depended for their results more on careful clinical observation than on laboratory reports He started his career with some initial advantages a family bias towards medicine, a fund of sound Scotch commonsense, a dry sense of humour, and—most important of all—a real love for children But the high position he reached in his chosen specialty was the result of steady hard work He first became known as a teacher at Guy's, and later to a wider circle, by his writings, for he was a ready writer and made many contributions to pædiatric literature Much the best known of these was his book on *The Nervous Child*, which is indeed almost a classic and is so delightfully written and contains so much sound sense and good advice that it can be put in the hands of even lay people interested in child guidance

Cameron was an ardent member of the British Pædiatric Association and one of his latest writings was a history of the Association published two or three years ago He rarely missed being present at the annual meeting of the B P A and was one of its most popular members, being admired by his fellows for his knowledge and beloved for his modesty and friendliness He will be much missed in the Association and indeed by the whole pædiatric world, but he has left an example in his character and work which should be an inspiration to those who follow him in the study and care of child health

R H

To pass down the Colonnade at Guy's for the first time and to cross the Park seemed to the university man in the early years of the present century only a familiar experience repeated, and when the Medical School had been gained, there awaited a welcome from a particularly charming don, the Dean himself This prepossessing person was Dr Hector Charles Cameron, a physician of Guy's and one of the men who upheld its fame, a pioneer in the art of medicine and a man of unsurpassed urbanity Though Cameron was well versed in scientific knowledge, he was more akin to a creative artist in mind By his power of perception he was able to apprehend the true and the beautiful, or in a word the good, by means of his imagination he related what he had perceived to human life, and the synthesis accomplished he gave expression to the idea through the art of medicine Out of such a philosophy, essentially Platonic, certain consequences must ensue The patient had to be seen as a whole, for health of mind and health of body are equally desirable and interdependent From that notion a practical psychology was formulated, which, less far-reaching than the modern variety, was a great deal more agreeable and wonderfully serviceable The bulk of this original doctrine he embodied in a book *The Nervous Child* which made his name known far and wide His ideas gradually shaped his career Having made a start as a general physician, as was the way, he found himself drawn towards mother and child, partly because they satisfy so well the aesthetic faculty, partly because they are plastic material, which holds out to the artist the promise of success Then, since an ideal conclusion is the business of our art as he conceived it, illness must be prevented as well as cured Finally, it would wrong him not to say plainly that a Platonic philosophy is an aspiration towards love Cameron was a true lover of his kind

-As a teacher he won great admiration He was always lucid, he never failed to interest, he had wit, wide reading and knowledge of the world, an easy eloquence and a polished style He charmed with his appearance and delightful courtesy, and with his artist's imagination he held his hearers The good that came from these ideal qualities was enhanced by two others not always their companions, industry to wit and practical ability It seems the natural thing today to gather the children into an outpatient department or house them in their own ward under the care of one who understands them, but Cameron had to accomplish these advances and was one of the first to do so Then with a fine stroke he founded a welfare centre in the precincts of the hospital Now only those who can set the child of forty years ago or more beside the handsome, happy creature of today can know what a revolution Cameron wrought, with others at his side

After his retirement he continued to exercise his pure and limpid prose *Joseph Lister the Friend of Man*, *Sir Joseph Banks the Autocrat of the Philosophers*, and his domestic history, *Mr Guy's Hospital*, are all valuable works He reached a hale old age, showing no alteration for years, and now that he is gone, it may seem commonplace to observe that he cannot be replaced Yet it is true, for the broad civilisation in which he was reared is being ousted by something very different *Damnosa quid non imminuit dies* ? But where he is concerned, who shall repine? He leaves the record of a fine vocation nobly fulfilled, great good accomplished, a blameless life and unswerving friendship

H St H V

Dr OLIVE STERN

R M. H writes

Olive Stern's background was richly cultural, which enhanced to the full her mental qualities She was incisive in expression and her construction was as fine as the finest rapier Naturally, this did not appeal to all, but to those who understood and appreciated it was just that diminutive creature who could smoke cigarettes, cigars, and a pipe and back her fancy in the Lincoln, Leger, National, and Derby She was spontaneously generous and one remembers with gratitude the hospitality extended in the delightful Old Billing home and later in Town " Petrol fumes " were the spice of life to her as they brought to mind her constant love—London—where with J G Greenfield, for whom she had a disciple's devotion, she was more than happy Her basic interest was neuropathology, but in general she was the vivid possessor of a tremendous wealth of detailed medical knowledge which proved invaluable to those who sought her opinion—and acted on it. Politically she was a bonny fighter and with the same undaunted courage she faced her final illness

SYLVANUS PERCIVAL VIVIAN

Kt, C B

Sir Sylvanus Vivian, formerly Registrar General, died on March 28 at the age of 77

In 1919 the General Register Office was brought within the province of the new Ministry of Health, and Vivian, who had worked in various departments of the Civil Service, was appointed Deputy Registrar General He succeeded Sir Berhard Mallet as Registrar General in 1921 and he supervised the census of England and Wales in that year and in 1931 His office was chiefly responsible for the compilation of the wartime National Register He was a member of the Boundary Commission in 1944 and retired in 1945, to be succeeded by Sir George North Outside his official life he had wide literary interests, and edited the works of Thomas Campion and contributed to encyclopædias

Appointments

EVANS G P A, M B Glasg, D P H deputy M O.H, Walsall

SAMUEL, ERIC, M D Lond, B SC Wales F R C S, F F R, D M R E head of the department of radiodiagnosis, Edinburgh Royal Infirmary

Notes and News

DIET AND HEART-DISEASE

The American Heart Association has issued to the public a leaflet on what is known and what is not known about the relation between diet and heart-disease It deals with fat, fads, sodium, and obesity—politely termed "overweight"

Readers are told that collections of fatty substances on the inside lining of the coronary arteries underlie most heart attacks, and that research is being done on whether changes in the diet can affect these, doctors may recommend low-fat or low-cholesterol diets in specific cases It is a mistake to listen to the tales of friends, relations, or popular magazines—"your health is much too precious to entrust to any person other than your doctor" Deposition of fat when more calories are absorbed than used is compared to piling up a bank account by depositing more than is withdrawn, but overweight, unlike a fat bank account, is not a good thing, because it adds to the work of the heart Sodium is essential to life, but its intake is sometimes restricted deliberately because in certain conditions it retains water in the body

The leaflet emphasises the importance of individual advice by a doctor in individual cases, it ends with five points to keep in mind—urging good general nutrition, efforts to keep weight normal, avoidance of special diets unless they are advised by a doctor, following a diet strictly where one has been prescribed, and asking a doctor's help about anything not understood

The Association's address is 44, East 23rd Street, New York 10, N Y, U S A

University of Cambridge

On March 22 the following degrees were conferred

M Chir—T W Rowntree, E J C Wynne
M B, B Chir—D E Side
M B—R C Dobbie (by proxy)

University of Birmingham

On July 5 the honorary degree of LL D is to be conferred on Dame Hilda Rose, a past president of the Royal College of Obstetricians and Gynæcologists, and the honorary degree of D SC on Prof A M B Lacassagne, director of the Radium Institute at the Pasteur Institute, Paris

Dr G H Thomas has been appointed senior lecturer in endocrine chemistry in the department of anatomy

University of Durham

On July 5 the honorary degree of D C L is to be conferred on Sir David Campbell, regius professor of materia medica and therapeutics in the University of Aberdeen and president of the General Medical Council

University of Leeds

At a recent examination O P Edmonds obtained the degree of M D

University of Dublin

The following have been awarded the diploma in gynæcology and obstetrics (D G O)

Mya Mya Aye, J O Toohey, F D Heelan, Khalida Abdul Wehab Al Kayssi, *J D Le Souef, Shalini Tanavde*

Royal College of Physicians of Ireland

On March 28 the following were granted the licence in medicine and midwifery

J G Bailie, Efiong Ekpo, J R McClean, Frances M U Power, Subhan Ally Ramjanally, R F Rampersad, J D Rautenbach, Ewa Wohnout

Royal College of Obstetricians and Gynæcologists

On Friday, May 30, at 5 P M, at the college, 58, Queen Anne Street, London, W 1, Mr J S Scott will give a William Blair-Bell lecture on pregnancy toxæmia associated with hydrops fœtalis, hydatidiform mole, and hydramnios Admission is by ticket which may be had from the secretary of the college

Central Midwives Board for Scotland

The medical members of the reconstituted board are as follows

Mr J Bruce Dewar (Dumfries), Prof David McKay Hart (Glasgow), Dr Catherine Harrower (Glasgow), Prof R A Lennie (Glasgow), and Dr Nora Wattie (Glasgow)

South West Metropolitan Regional Hospital Board

The following have been awarded prizes in the board's 1957 competition

Consultants and S H M Os—Dr A A Cunningham and Dr J Towers
Senior registrars, registrars and J H M Os—Mr J C Gazet, Dr A J Taylor, Mr P W Seargeant, Dr J R H Pinkerton, and Dr P Farnan
Senior house officers—No entries received

Notice of entry for this year's competition (with proposed subject) should be sent to the board's senior administrative medical officer (Gen /CST) by Sept 30, and reports must reach him by Dec 31

British Association of Pædiatric Surgeons

The annual meeting of this association will be held in London from July 23 to 25 On Wednesday, July 23, at 5 30 P M, Dr Willis Potts, from Chicago, will give the Simpson-Smith lecture on tracheoœsophageal fistula with and without atresia, and on Friday, July 25, at 4 30 P M the Moynihan lecture on respiratory emergencies in the newborn Further particulars may be had from Mr R B Zachary, The Children's Hospital, Sheffield, 10

Royal Commission on Remuneration

The Royal Commission on Doctors' and Dentists' Remuneration will hold a public hearing on Thursday, April 17, at 10, Carlton House Terrace, London, S W 1 Representatives of the Ministry of Health, the Department of Health for Scotland, and the Treasury have been invited to attend The hearing will begin at 11 15 A M and is likely to continue into the following day

Industrial Health and Accident Prevention

A conference on this subject, organised by the Industrial Welfare Society with the support of the Scottish Industrial Groups Advisory Council and the Association of Industrial Medical Officers, will be held at the St Enoch Hotel, Glasgow, on April 30 The speakers will include Dr Andrew Meiklejohn, Dr J H Bell, and Dr A Girdwood Fergusson

Portrait of Sir Alexander Fleming

On March 26 at St Mary's Hospital, London, Prof C A Pannett unveiled a portrait of the late Sir Alexander Fleming, by Miss Anna Zinkeisen, which is to hang in the boardroom of the hospital It was remarkable, he said, that though St Mary's is little more than a hundred years old and has possessed scientific laboratories for only a fraction of that time, already two workers in those laboratories have attained imperishable fame, and both by saving countless human lives—Almroth Wright by his invention of anti-typhoid inoculation and Alexander Fleming by his discovery of penicillin To those who knew them it was a sad and chastening thought that to neither had been raised a great scientific institute, nor had there been created, as a tribute to their memory, a scientific foundation in any way commensurate with the benefits they had conferred on the hospital and the world The same treatment had been handed out to Jenner, and it was typical of the English indifference to great men and particularly to the humble scientist However, this portrait, commissioned by the governing board, was impressive and successful, a superb piece of craftsmanship, and as Sir Alexander gazed down on the members in their deliberations, they would be aware of the greatness of St Mary's and the nobility of their task

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On *Monday, April 14, at 7 30 P M at 5, Old Burlington Street, London, W 1, the Society for Visiting Scientists will hold a meeting* on Personality The speakers will be Prof Marc Klein, of Strasbourg, Dr W Mays, and Dr J D Sutherland

A meeting of the Naval Medical Compassionate Fund will be held at 2 30 P M on Friday, May 2, at the Medical Department of the Navy, Queen Anne's Mansions, St James's Park, London, S W 1, to elect six directors of the Fund

The first volume of the new edition of the *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death* appeared last October (see *Lancet*, 1957, ii, 882) and came into force at the beginning of this year The second volume, an alphabetical index, has now appeared, and is obtainable from H M Stationery Office The two volumes together cost 35s

The Lancet · Saturday 19 April 1958

ADMINISTRATIVE THERAPY
ITS CLINICAL IMPORTANCE IN THE MENTAL HOSPITAL *

D H CLARK
M A Cantab, M B Edin, M R C P.E, D.P M
MEDICAL SUPERINTENDENT, FULBOURN HOSPITAL, CAMBRIDGE

PSYCHIATRY today is becoming steadily more specialised, and the day of the old-time medical superintendent who was master of all possible trades within the asylum has passed. He was at once senior psychiatrist, consultant physician, medicolegal expert, morbid pathologist, and general practitioner to the resident staff. Today no-one is called upon to exercise all these skills, and there is a chance to examine afresh the work and role of the medical superintendent and see what therapeutic possibilities they offer. From my attempt to study this I have emerged with a concept of Administrative Therapy—the art (perhaps some day to be a science) of treating psychiatric patients in a mental hospital by administrative action. Group therapy developed from individual therapy, administrative therapy is treatment of a much larger group, the hospital. It draws on the knowledge and skills of psychiatry and group psychotherapy, the experience of the professional administrators, and the accumulating contributions of the social anthropologists.

The Administrative Role

What does the role of medical superintendent mean to the doctor who undertakes it? What limitations and obligations does it place on him? Every psychiatrist cherishes a fantasy of what he would do if he were medical superintendent of his hospital, the essence of this fantasy is the delusion that the medical superintendent is omnipotent and can do anything he wishes. A doctor who becomes medical superintendent soon finds out how limited he is, there are so many things that he cannot do or that take a long, long time. There are the obvious limitations which block his programme—shortage of money, ancient buildings, overcrowded wards, shortage of nurses, not enough doctors, conservatism of those long in office, limitations of Treasury finance, and the tremendous difficulty (in the complex organisation of the National Health Service) of getting any new idea accepted. All these things are well known and understood. Underlying them all is the inertia of any large human organisation, which is the sum of the unwillingness of many people to change their ways.

More limiting than the things he cannot do, however, are the things he must do. Every administrator must carry out a number of ritual public actions which can be performed by no-one else, they may be disturbing, frustrating, or merely boring, but he must do them. It is in this context that the word "role" which we use so glibly approximates most closely to its theatrical meaning, for the leader of any organisation has to perform certain acts which are prescribed for him and for which he may personally have little taste. He is the figurehead, the spokesman, and at times the voice of conscience, these duties take up time which he often feels to be wasted, for they give him no feeling of achievement and certainly none of "proper work."

As figurehead he must function on public occasions, making speeches, setting forth the principles of the organisation, proposing votes of thanks graciously, he must offer public congratulations, he must make presentations to the employees who have been a long time in the hospital, he must speak at nurses' days and at the opening of new buildings. At all these times he must express the feelings of the staff and the patients and yet at the same time draw out unifying themes and suggest future goals. He must act as chairman of certain essential coordinating committees within the hospital, where departments are in conflict and only he can mediate. It is only reasonable to hand over some of these tasks to others, but he must beware how often he does this, he must remember that there is always a loss of definition when he does.

There are aspects of the role which may be frankly repugnant, especially to a sensitive psychotherapist. Promotion must be made, every time one person is gratified by promotion several are dissatisfied or even embittered. When someone breaks the rules, the administrator must not shirk the unpleasant duty of seeing the errant offender, cautioning him, and if necessary discharging him. Much can be done to obviate social disturbance by fair dealing, by constant self-scrutiny, and by willingness to admit mistakes, but there comes a time when someone must pronounce the community disapproval of an individual's actions, and the leader of the community forfeits its confidence and weakens it if he is not prepared to do this.

The administrator should not actively seek transgressors, seeking transgressors is an antitherapeutic activity best left to those whose task it is, such as auditors. If communications are free, malpractices soon come to light, if an irregular procedure gives no-one cause for complaint, then there is little need to seek it out. If an administrator spends his time checking his juniors, he conforms to the traditional asylum stereotype of fault-finding authority and soon paralyses the hospital. His task is the more difficult one of seeking out and encouraging initiative and therapeutic development.

The doctor who becomes medical superintendent will learn some of the lessons and pains of administration. He will find folklore and fantasy condensing about him whatever he does, so that he will be credited by some with magical prescience and wisdom, and by others with malignant cruelty and foolishness. He will find injustice and even tyranny exacted in his name. He will learn the gratification of seeing a change, long fought for, produce the desired result, and the bitterness of espousing and effecting a change only to see it fail because of flaws he had not perceived. He will learn how long it takes to bring about a change, how change imposed is of little value, how patience and a sense of timing often achieve more than enthusiasm.

The role of medical superintendent, like every other worth-while role in life, will have a moulding effect on him. To the characteristics developed by years of medical responsibility will be added characteristics of the wielder of power—the cautious utterance, the guarded promise, the ready excuse that saves the need of self-scrutiny, the specious justification, the growing pomposity and intolerance of criticism, the diminution of scientific detachment. All these will come, and his friends and colleagues will commiserate with his wife as they become more obvious.

Medical or Lay?

These are some of the experiences and problems that face any administrator. Is a doctor, a psychiatrist, the person to undertake them? Administration of general hospitals is carried out by non-medical professionals in England (though not in Scotland), some of them have

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* Based on an address to the psychotherapy and social-psychiatry section of the Royal Medico-Psychological Association on Oct. 9, 1957

pressed strongly that the mental hospitals would also be better out of the hands of the doctors—though they state this as an altruistic desire to "free the doctors for their proper work" The debate often reaches a high pitch of acrimony as the well-organised and vocal groups battle for privilege and power, many of the arguments are specious, transparently self-interested, and valueless except as debating points But the question must be considered A bad administrator is a disaster for any hospital, be he medical or lay—and examples of both are easy to find in English hospitals Their faults are different but equally pernicious The bad lay administrator is a petty-minded bureaucrat, ruled by regulations, frightened of responsibility, and insensitive to human needs, the bad medical administrator is a patient-centred doctor who regards administration with contempt, who lacks the ability to plan and think ahead, the courage to face group situations, and the imagination to understand the problems of non-medical professional groups

Any doctor who undertakes to be an administrator must accept what that means He must be prepared to learn something of administration, he must have an interest and ability in handling, leading, and uniting people He must be tolerant of the status systems of professions other than his own, and understand that coming in by the front door, or wearing a collar, may mean as much to someone as the right to a long white coat once did to him He must learn a smattering of many jargons He must lend an interested ear to the catering officer, the engineer, and the garden manager, and must understand what pains them He must, too, be ready to think seriously about the structure of authority and organisation, it is not enough to rely on traditional modes of direction

Doctors do not generally make very good administrators All their training has been away from this, and if a doctor is a good administrator it is because a talent for handling groups and an interest in working with them has survived his medical training Throughout the medical training, skill is developed towards a two-person situation, and a very special two-person situation—the handling of a patient who is often socially and intellectually inferior to the doctor, and, if he is not, is unmanned by anxiety, pain, and fear of death The doctor is the expert whose words are weighty and powerful, his verdict is the utterance of a judge The psychiatrist and the psychotherapist are further trained to think of the individual patient and his good, but seldom of the good of the community or the group

The doctor with experience of group or social therapy comes to administration with an advantage He has learnt to think in terms of the group rather than the individual, he has already begun to swing away from the exclusive one-patient orientation of the traditional doctor and traditional psychotherapist This is of great value when he comes to administration, where every decision has to take into account the needs of a number of individuals In his group therapy he has acquired an ability to handle the group situation, which again is valuable Many medical superintendents never acquire this when they are alone with a patient or with a junior doctor they are competent and powerful, when faced by a group they become anxious, secretive, and fear-ridden A group therapist, however, should have worked through this He can sit among a dozen other people, watch what they are doing, listen to what they are saying, and contain the anxiety that arises in him when heavy hostility or pressure is directed against him, he can feel what is happening, engage in the interaction, and yet keep sufficiently apart to observe it and wait his time for joining in

The psychiatric administrator has to take part in one group which is an entirely new experience to him—the management committee Here he is not the leader, the therapist doctor, the omnipotent expert, he is not even a member of the committee, he has no power to vote, he is merely an official The determination of policy is in the hands of the committee

This role comes hard to doctors, for they are accustomed to being experts, and the experience of working with lay committees can be peculiarly disturbing for them Perhaps for the first time since he entered medical school the doctor meets laity who may not be much impressed by his statements and can say so, who do not credit him with omniscience Those fascinating and admirable people who give constant and assiduous voluntary service on committees have limited respect for experts of any kind, including doctors They themselves are magistrates, town councillors, and aldermen, accustomed to judge the affairs of their fellow men and make decisions affecting the lives of others They have often heard experts explain with specious technical jargon why certain courses must be followed, and they are no longer to be taken in They have seen through borough surveyors, have deflated headmasters, and have goaded medical officers of health into action, they are little impressed by oracular certainties If the medical superintendent wishes to carry the management committee with him he must learn to justify his policies on sound well-based grounds of the general good They will allow the doctor his full meed of expert knowledge but if he wishes to spend more public money, he must show good reason why

The Fabric of Human Relations

The third report of the World Health Organisation's Expert Committee on Mental Health[1] said that the most important single factor in the efficacy of the treatment given in a mental hospital is "an intangible element which can only be described as its atmosphere" They gave in detail some of the elements which make up that atmosphere, and went on to say

> "As in the community at large, one of the most characteristic aspects of the psychiatric hospital is the type of relationship between people that are to be found within it, the nature of the relationships between the Medical Director and his staff will be reflected in the relationships between the psychiatric staff and the nurses and finally in the relationship not only between the nurses and the patients but between the patients themselves"

This is a challenging statement, and contains the kernel of administrative therapy—which may be defined as the manipulation, modification, and constant scrutiny of the relationships spreading out from the administrator, with the aim of controlling their effect on the patients

Administrative therapy is in much the same state as psychotherapy was in the 1880s At that time many doctors, neurologists, and alienists were talking to patients about their lives and their problems and helping them, some were exhorting patients to follow different modes of behaviour and by that exhortation were improving their adjustment to life There was, however, no awareness of what they were doing, no insight into the factors concerned, and such instructions as they gave were based on self-evident principles. Then Freud showed how much more went on between the doctor and the patient, and interpersonal reactions began to be explored. After fifty years we are now at last beginning to understand something of the dynamics of the two-person therapeutic situation. Administrators at present tend to handle their organisations with as much insight as Charcot used with his hysterics, they proceed from intuition, self-evident deductions, and political theory, their only guide being catchwords and slogans. We need to study how actions and activities of the administrators finally affect the patients, and (more important) learn how to alter these actions therapeutically. In this way we shall develop some knowledge of administrative therapy.

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[1] World Health Organisation Third report of the Expert Committee on Mental Health Geneva, 1953

The fathers of institutional psychiatry had no doubt in their minds about the importance of administrative therapy though they called it "moral management". One has only to read Tuke's *Description of the Retreat*[2] or Pinel's *Treatise on Insanity*[3] to see the importance they give to the management of the house, both stressed how unimportant formal medicine is and how useless drugs, bleeding, and purgation. Both of them discussed with admiration the work of the men who ran their hospitals, Pinel rapturised about Pussin, Tuke soberly praised the skill and consideration of Jepson, both devoted large sections in their books to describing just how the asylum should be organised and the rules that should be laid down for the life of the patients.

In each generation reformers arose, like Kirkbride in America and Simon in Germany, who restated some of the principles, occasionally with an individual twist of their own, they were heard for a time, and then they were forgotten and dropped away. The W.H.O. report sets out the principles yet again, and they are very similar to those of Tuke and Pinel. Patients are to be trusted and given as much freedom and responsibility as possible, their individualities must be preserved, and the life in hospital made as much like that outside as possible, particularly by providing regular planned and sustained activity and employment.

Four Principles

When a psychiatrist decides to become a medical superintendent how can he look at his job? What are the principles that he is to follow? There are four main facets of administrative therapy:

1. Organisation of the patient's life.
2. Staff organisation.
3. Medical organisation.
4. Community leadership.

These are, of course, interlinked, and maladroitness in one affects the others, but they are in some degree separate. Of every action one must ask the dynamic questions. How was it done? Did it have the effect desired? What other side-effects did it have? Did it help the patients?

Patient's Life

The first is perhaps the easiest of the four, for a great deal is known about it. The ideas of moral treatment and the principles put forward by the W.H.O. report give a start. It would take several years' work in any hospital to get these accepted as a fundamental way of life. The abolition of restraint, seclusion, locked doors, and over-sedation is the first move. Proper segregation into wards each with a definite function is of great value. Diligent organisation of a full work therapy programme for all patients in the hospital takes time and it must include a proper system of rewards and payments. These first essentials can be fairly easily achieved over a few years, though a close guard must be kept against the custodialism which is forever creeping back under the guise of economy and "efficiency". Next comes the development of self-government for the patients and experiments in communal living—group therapy, discussion groups, play-reading, hospital magazines, and mixed units.

Staff Organisation

To organise a therapeutic staff is more difficult. The staff in any mental hospital has been trained for years in custodial attitudes, they were trained to count patients and to watch stock, they learnt that an escape was the most awful sin—worse even than a suicide or an accident—and they have acquired whole series of custodial and often punitive reflexes that are not easily abandoned. In most hospitals, too, there is a rigid hierarchial system with orders passed down from above and a severe blockage on the flow of information upwards, there are usually rigid status barriers between the different categories of staff. The administrative therapist must decide what to tackle first. He cannot just plunge in naïvely with the ideas of making everybody democratic, if he endangers the security of senior staff, he himself may be extruded.

The emphasis should be first on communication. Meetings should be held with various groups of staff and they should be encouraged to bring forward ideas, through such meetings new channels of communication can be laid down. It is a grave mistake to come to the conclusion that some person or other is nothing but a bar to all progress and to attempt to "drive him out". If your patients are to have human dignity, your staff must have it too. The only correct assumption is that everyone has something to contribute and that given the chance he will do his best.

Questions of responsibility and authority are central and must be constantly studied. In most mental hospitals there is scope for far wider devolution of responsibility.

Medical Organisation

The administrative therapist must give special thought to the organisation of the doctors. They may have little interest in his abilities as a social therapist, but they wish to believe that he can practise their art of clinical psychiatry at least moderately well. The medical superintendent should continue to see his own cases and have cases within the wards, otherwise he will no longer understand his colleagues' problems. The relations of the administrative therapist with the consultant psychiatrists are a difficult and testing point. At present there is much pain and bitterness about this in English mental hospitals. Some medical superintendents still think in terms of the pre-1948 situation, when the medical superintendent was personally responsible for the treatment of every patient. Today the consultant psychiatrist has full responsibility before the Law and before society for the treatment of his patients, and there can be no excuse for the medical superintendent interfering in the treatment prescribed. But the issue goes deeper. The consultant psychiatrists are the only group of peers whom the medical superintendent meets, the only group who share his professional training. Many consultant psychiatrists despise administration and do not think much of administrative therapy or social psychiatry. What they want to do is to treat individual patients in the one-doctor/one-patient relationship, this they think of as the highest good. The administrative therapist's task is to provide a milieu in which everyone may do his chosen job to the best of his ability without interference, and this is as true of the consultant psychiatrist as of humbler people in the organisation. If an administrative therapist does his own job well and takes the same care to avoid trespassing on another doctor's patients that is standard throughout medicine, his relations with his consultant staff should be good. If he can provide them with the facilities they need to do their work, free of the more vexatious hospital irritations, he will gain their gratitude and respect.

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[2] Tuke, S. A Description of the Retreat. York, 1813.
[3] Pinel, P. A Treatise on Insanity. London, 1806.

The medical organisation will vary with the size of the hospital It has been suggested that the best size of unit for administrative therapy is about 300 beds, it is still just possible to administer 1000 beds as a unit With larger hospitals, however, the span becomes too great and it is necessary to split the hospital into “ firms ” running self-contained units with a consultant and senior nursing officer in charge The only difficulty with this is that differing cultures develop in the self-contained units, if they differ too much, it is hard for patients and junior nurses to understand that one institution can have such different units within it, and they may find the passage awkward from a liberal environment to a restrictive one

Community Leadership

If any human organisation is to work well, it should have confidence in itself, it should have a policy, and it should have good morale The administrative therapist must give these to the hospital as best he can The hospital policy must be clearly formulated In the past the cries have been “ non-restraint ” and “ full activity ”, recently it has been “ open doors ” The policies of the W H O report must be worked into the structure of the hospital and embodied in slogans which can be understood by the most uninterested staff member They must be repeated again and again until they really have meaning and until the words “ therapeutic community ” mean not just the bee in the superintendent's bonnet but a way of living and acting

Relations upward are always difficult, and it is in this sphere that some social therapists fail sadly, while some autocratic medical superintendents have often been quite successful The hospital management committee decide the policy of the hospital, if an administrative therapist is going to change the whole life and way of a hospital he must carry the management committee with him They are mature and tend to conservatism, they are dubious about the enthusiasms of youth and many have much previous experience of the hospital They must be won to new policies which must be put to them in terms of the humanitarian gain to the patient, for in this they are always interested Beyond them the policy must be carried to the public, it is no use opening your doors if the local public and the police shout to have them locked again In this the cooperation of the local press is vital and the administrative therapist must work with them Cheerful reports about the hospital will dispel criticism, will build up the morale of the staff, and will do much to allay public anxieties

In an N H S Setting

Within the National Health Service there is constant work to do Though new buildings do not produce good psychiatric treatment, some new equipment is needed for the hospital, and the hospital which feels that it gets the last handout of everything may become dispirited The administrative therapist as leader of the hospital and spokesman for its policy must be prepared to argue policy up the various tiers of the National Health Service, this involves knowledge of local power relationships and a willingness to explain again and again things which seem crystal clear It needs patience and self-control to put over an idea, which is of great personal importance, to a committee who are perhaps uninterested or committed to the needs of another hospital, and to carry conviction so that the needed money is granted

There is also a constant defensive battle to be fought, ever busy within the fabric of the National Health Service are those white ants, the auditors, nibbling away and eroding the fabric of human relations and good feeling They are employed to peer through every hospital attempting to prove that everyone is dishonest and that no-one can be trusted, given their way they would multiply the regulations until the hospital was bound in a cocoon of red-tape, all in the name of “ efficiency ” They must be watched unceasingly and every claimed advance in efficiency scrutinised with great care to see it does not harm the human relations of the hospital Luckily they too are only servants, and the masters are the hospital management committee, the representatives of the public, if an administrative therapist is worth his salt he can carry the point against the auditors and show that the welfare of the patients and the trust and happiness of the staff are first essentials

But the most important task of the administrative therapist is to establish the atmosphere of the hospital And this, the most important, is the task most difficult to describe He needs openness, consistency, respect for everyone's human dignity, and a welcome for everyone's contribution, a belief that everyone wishes to help and that no-one is past recovery—neither the most demented patient nor the most stupid nurse For one thing is certain as he treats his staff so will they treat the patients

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These are some of the aspects and personal meanings of the art of Administrative Therapy as they strike one new to the field, but there is so much to learn Studies like those of Stanton and Schwartz[4] point the way to an understanding of the dynamics and the effects of administrative action By such means, knowledge may gradually replace intuition until the art becomes a science

THE AUTOANTIBODY NATURE OF THE THYROIDITIS ANTIBODY AND THE ROLE OF THYROGLOBULIN IN THE REACTION

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ASSISTANT PROFESSOR OF BACTERIOLOGY AND IMMUNOLOGY

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From the Department of Bacteriology and Immunology, University of Buffalo School of Medicine, and the Buffalo General Hospital, Buffalo, New York

In rabbits, dogs, and guineapigs, intradermal injection of thyroid extract (combined with Freund adjuvants) from other animals of the same species engenders the production of organ-specific thyroid antibodies, as well as an accompanying thyroiditis (Witebsky and Rose 1956, Rose and Witebsky 1956, Witebsky et al 1956) An extract of the animal's own thyroid gland has the same effects Moreover, the serum of some patients with chronic non-infectious thyroiditis contains a factor that reacts with human thyroid extract, normal or goitrous (Roitt et al 1956, Witebsky et al 1957, Paine et al 1957, Doniach and Roitt 1957) On the basis of the animal experiments, it has been proposed that this serum factor is a true autoantibody, and that the pathogenesis of the clinical disease is related to autoimmunisation Additional evidence for the autoantibody nature of the serum factor is found in experiments in which thyroid extracts from numerous different individuals exhibited essentially identical titres when tested with a thyroiditis serum (Witebsky 1957) The criteria for establishing the existence of antoantibodies have been discussed by us previously (Witebsky et al 1957)

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[4] Stanton, A , Schwartz, M The Mental Hospital London 1955

TABLE I—RESULTS OF TANNED-CELL HÆMAGGLUTINATION TEST

Dilutions of Buc serum	Tannic-acid-treated human erythrocytes (group O) coated with saline extract* of	
	Buc. goitre	Het. goitre
1 20	+++†	+++
1 40	++	+++
1 80	++	++
1 160	++	++
1 320	++	++
1 640	±	±
1 1280	±	–
1 2560	–	–
control‡	–	–

* Each extract diluted 1 100 and immersed in boiling water for 2 minutes

† +++ to – indicates various degrees of agglutination of erythrocytes after tubes were allowed to stand overnight at 4°C.

‡ Tanned but uncoated cells Other controls using normal human sera rather than patient s serum were uniformly negative.

Nevertheless, as Cruickshank et al (1957) have emphasised, an important step in establishing the presence of a true autoantibody (rather than an isoantibody) is the demonstration of a reaction with the patient's own tissues Mackay, Larkin, and Burnet (1957) have pointed to the failure of certain so-called autoimmune antibodies to react with antigens prepared from the individual's own tissues We therefore report here an experiment illustrating just such an in-vitro reaction

Observations

A patient, Mrs Buc, was operated on at the Buffalo General Hospital in October, 1956, when a large diffuse colloid goitre was removed A sample of her serum taken at this time (Oct 23, 1956), when examined by the tanned-cell hæmagglutination and precipitation methods, revealed no trace of thyroid antibodies The surgically removed tissue was stored in the frozen state.

Taken four months later (March 15, 1957), a second sample of her serum produced a positive reaction in the tanned-cell hæmagglutination test for thyroid antibodies (titre 700) using pooled normal human thyroid extracts as antigen Precipitation tests were negative (A sample of her serum, taken in December, 1957, revealed a slight decrease in antibody titre—500) The possible clinical significance of the postoperative appearance of antibodies in this case has been discussed by Paine et al (1957)

The patient's thyroid tissue obtained previously was thawed, and a saline extract was prepared by our usual technique A similar extract was prepared from a second surgically removed non-toxic goitre (Het), and both goitre extracts were used as antigens in a tanned-cell hæmagglutination test of a sample of Buc serum The results of the test are given in table I, which shows that the patient's serum agglutinated human erythrocytes coated with an extract of her own goitre as well as the goitre extract of another person, Het The titres in each case are the same within experimental variation, and resemble those obtained in other experiments with a pool of thyroid extracts

TABLE II—ULTRACENTRIFUGAL ANALYSIS OF PATIENT'S THYROID EXTRACT AND FRACTIONS

Fraction	Concentration (total protein) (g per 100ml.)	Peak	Analysis (%)	Total thyroglobulin (g per 100 ml)
Initial saline extract	4·07	I	4·51	
		II	52·4	2 13
		III	1 53	
		IV+V	41·5	
P 1 60–1 70* (' thyroglobulin)	2 48	I	2·45	
		II	94 6	2 23
		IV+V	2 99	
P 1 70–4·00†	1·93			
RP 2·50–3·00 (thyralbumin)	1 16	V	100·0	

* Precipitate obtained between 1·60 and 1 70 M ammonium sulphate.

† Residual proteins after precipitation of thyroglobulin fraction.

We conclude, therefore, that the thyroid antigen involved was actually present in the tissues of the patient, as well as in the thyroid glands of other persons

Discussion

Which constituent of the thyroid extract is responsible for the reaction observed? Our preceding investigations (Witebsky et al 1955, Rose and Witebsky 1955, Shulman et al 1955) on the organ-specific nature of thyroglobulin suggested to us that, in animals, it would play the leading role in autoimmunisation Similarly, Roitt, Doniach, Campbell, and Hudson (1956) have regarded thyroglobulin as the important antigen in human thyroiditis To study this point further, the Buc extract was fractionated by addition of ammonium sulphate in the same manner as previously described for hog-thyroid extract (Shulman 1956, Shulman et al 1957) Ultracentrifugal analysis of the initial saline extract revealed at least five sedimenting components (table II), of which one, peak II, was identified with the classical thyroglobulin on the basis of its sedimentation constant These sedimenting components seem to be completely analogous to those observed in hog preparations (Shulman et al 1955, Witebsky et al 1956) The portion of thyroid extract precipitating between 1 60 and 1 70 M ammonium sulphate shows a relative enrichment in thyroglobulin content and a considerable decrease in content of peaks I, III, IV, and V The only other ultracentrifugal component available in purified form is peak V, the thyralbumin fraction, obtained by precipitation between 2 50 and 3 00 M ammonium sulphate (Shulman et al 1957)

TABLE III—INHIBITION OF PATIENT'S SERUM BY VARIOUS THYROID FRACTIONS

Fractions of Buc thyroid	Antigen dilution
Initial saline extract	1 128 000
P 1 60–1 70 (thyroglobulin)	1 64,000
Residual supernatant (P 1 70–4 00)	1 4000
P 2 50–3·00 (' thyralbumin ')	1 80
Norman human kidney extract	0*

* No inhibition with undiluted extract

To measure the antigen content of the various thyroid fractions agglutination-inhibition tests were set up Serial dilutions of each fraction were prepared and added to aliquots of the Buc serum diluted to contain about four (2+) hæmagglutination doses After an hour at room temperature tanned human red cells coated with the Buc thyroid extract were added to each tube, and the degree of agglutination was read in the usual way

Table III shows the highest dilution of each thyroid component capable of completely inhibiting agglutination The initial saline extract, as well as the thyroglobulin fraction, can neutralise the reaction of Buc serum in high dilutions and are almost equally effective The thyralbumin fraction and the supernatant from the thyroglobulin precipitation show relatively little activity

These findings suggest that the antigen involved in the autoimmunisation leading to thyroiditis precipitates in the thyroglobulin fraction, and that this antigen can elicit demonstrable circulating antibodies in the same individual

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references overleaf

PRE-EPIDEMIC ANTIBODY AGAINST 1957 STRAIN OF ASIATIC INFLUENZA

IN SERUM OF OLDER PEOPLE LIVING IN THE NETHERLANDS

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After a strain of Asiatic influenza (A/Asia/Singapore/1/57) had been received by us at the end of May, 1957, from Dr C H Andrewes, of the National Institute of Medical Research, London, it soon became clear, using ferret antisera, that there was no cross-overlapping of surface hæmagglutinins between the egg line of this strain and the ferret-mouse-egg lines, egg lines, and egg-mouse-egg-lines of human A strains isolated in 1933–56 or a strain of swine influenza (Swine/15) isolated by Shope (1931) Similar observations were made by Meyer et al (1957), Jensen (1957), and Dr A Isaacs, of the National Institute of Medical Research, London (personal communication) Later it was shown that the same holds true for the mouse-lung-adapted line of the Asiatic strain

When, however, a few paired sera from patients who had had influenza in 1953 were tested against the Asiatic strain, one hæmagglutination-inhibiting titre of 44 was found in a serum taken during the acute phase of the disease in a patient aged 88 Next, of 12 sera from persons aged 59–84 2 from persons aged 80 and 84 showed a positive titre

With the aid of many doctors in the Netherlands we collected in June as many sera as possible from people aged 50–100 We already had in our laboratory sera from the younger age-groups Altogether 1256 sera were collected and stored at −20°C Through Dr A M M Payne, chief of the Section of Endemo-Epidemic Diseases of the World Health Organisation at Geneva, other laboratories in the world were asked to collaborate in this investigation and to collect sera as soon as possible before the Asiatic influenza had spread into their country In the Netherlands we were just in time, because the epidemic in this country started with its first focus in the middle of June

Methods and Materials

Hæmagglutination-inhibition (H I) Test

Sera were examined individually for H I antibody against the strain A/Asia/Japan/305/1957 (passage formula egg_x-ferret_3-mouse_6-egg_n) obtained from Dr K Jensen In our experience this is a more sensitive strain for this purpose than the egg-line of the strain A/Asia/Singapore/1/57 (Dr K Jensen, personal communication)

The titres of positive sera are expressed as the *reciprocal* of the dilution of the serum interacting with the virus and giving 50% hæmagglutination, being finally corrected to the use of 3 agglutinating units (A U) of the virus The non-specific inhibition of the sera was abolished by the use of enzymes of *Vibrio choleræ* (see Brans et al 1953)

After the screening of the sera had been finished, all the positive specimens were re-examined on the same day by two different workers The final H I titre was considered to be the arithmetical mean of the titres obtained in both tests Usually the titres in this final control did not differ substantially from those obtained in the screening test, the only exception being a few very low titres which in the final test proved negative Low titres were read with great care because pattern formation in low dilutions of sera not containing H I antibody may be incomplete

After the investigation had been finished, the ages of most of the people aged 70–100 who showed a positive H I titre were checked

Mouse-protection (M P) Test

In the M P test the strain A/Asia/Ned /43/57 (passage formula mouse_{22}-egg_{1-4}) was used This strain is identical with A/Asia/Japan/305/57 in the cross-H I test From the emulsion of infective mouse lung of the 22nd passage the strain was grown in the allantoic cavity of the chick embryo, and the egg fluid was used in the M P test The advantages of this method are that constant amounts of virus can be used in the different tests, and that the virulence of the virus can be maintained more or less constant M L D of about either 50 or 5 were used according to the H I titre of human serum, because usually H I titres below 30 could only be confirmed as true antibody in the M P test when fluids of low virulence were used

TABLE I—INCIDENCE OF PRE-EPIDEMIC POSITIVE H I TITRES IN HUMAN SERA OF DIFFERENT AGE-GROUPS AGAINST INFLUENZA STRAIN—A/JAPAN/305/57

Age-group (yr)	No of sera	No giving positive H I test
1–9	11	0
10–19	30	0
20–29	72	0
30–39	85	1 *(1 2%)*
40–49	121	2 *(1 7%)*
50–59	163	2 *(1 2%)*
60–69	361	4 *(1 1%)*
70–79	280	14 *(5 0%)*
80–89	122	27 *(22 0%)*
99–100	11	2 *(18 0%)*
Total	1256	52

We used as control sera in each experiment homologous ferret antiserum and the sera of two persons aged 24 containing antibodies against many former human A strains except the Asiatic strain In a second experiment it was shown that neither high-titred ferret antisera against the influenza strain A/Swine/15 nor against the egg- and mouse-lines of all the main types of former human influenza-A strains protected mice against infection with the Asiatic strain Six mice were used per dilution of serum, but in most of the experiments only the serum dilution 1 2 was used Necropsy on surviving mice was done 7–10 days after inoculation, according to the number of M L D used in the experiment

Complement-fixation (C F) Test with Soluble Antigen of Influenza Virus A

This test was made according to Hoyle (1948), egg-membranes being used for preparing the antigen

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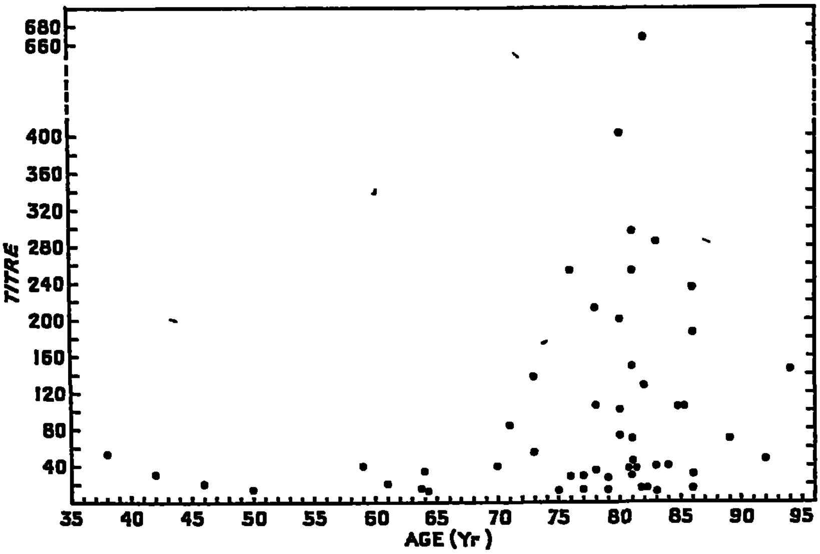

Fig 1—Age-distribution and positive H.I. antibody titre against influenza strain A/Asia/Japan/305/57 found in 1256 normal sera collected in Holland before July, 1957 (titres of <8 not incorporated)

Results

Positive H I titres were found in 52 of the 1256 sera examined In the sera from persons aged 71 or more there was an increase in number of positive titres (table I and fig 1) The total absence of positive sera in the age-group under 30 may be due to the relatively few sera available from this group There can be no doubt that the positive H I titres represent true antibody, as is shown by the results obtained with the M P test (tables II and III) Nor can it be assumed that recent infection with the Asiatic strain type of 1957 is concerned, because of the results with the C F test with soluble antigen of influenza virus A The first somewhat higher titre (87) was found in a person aged 71, and the first high titre (140) in a person aged 73 The youngest person with H I antibody was aged 39 (titre 54) The greatest incidence of positive titres was in persons aged 81 (8 of the 21 sera of this group showed inhibition)

Comparative titration of 49 positive sera against the Asiatic strain A/Japan/305/57, the strain A/Swine/15 and the mouse-adapted lines of 8 human A-strains from the period 1933–56 showed that in 17 sera (35%) the titre to the Asistic strain was higher than to any of the former strains (corresponding ages 76–94) In 2 sera a titre was present only to the Asiatic strain (corresponding ages 79–86) In 8 other sera the titre to the Asiatic strain was either about as high as the titre to one or more of the former strains, or amounted at least to 50% of the highest titre to one of these strains (corresponding ages 77–84) This finding is important, because it proves that in the ages 76–94 the Asiatic titres cannot in general be considered as having been caused by possibly existing shared minor antigen with known former strain types (see later) Meanwhile Davoli and Corsi (1957) have found pre-epidemic antibody to the Asiatic strain in Italian people, predominantly in the age-group 78–85

TABLE II—M P TEST AND C F TEST WITH SOLUBLE ANTIGEN A WITH HUMAN SERA SHOWING POSITIVE H I TITRE AGAINST INFLUENZA STRAIN A/ASIA/JAPAN/305/57

No of positive H I human sera	Mouse-protection test		C.F test with soluble antigen A		
	No positive	No doubtful	No negative	No doubtful	Serum showing own inhibition
52	25[1]	2[2]	45[3]	2[4]	4

1 Complete or incomplete protection in serum dilution from 1 2 to 1 8
2 H I titres 13 and 20
3 Titres from <1 8 to 1 16
4 Dilution 1 32, fixation ++, and dilution 1 64, negative.

TABLE III—MOUSE PROTECTION TESTS

H I titre	Age (yr)	Dilution of patient s serum				Dilution of Control Sera
		1 2	1 8	1 32	1 128	1 2
87	71	++ + 0 0 0 0	++++(D) ++++(D) +++ ++ 0 0	++++(D) ++++(D) ++++(D) ++++(D)	++++(D) ++++(D) ++++(D) ++++(D) ++++(D) −+++(D)	++++(D)×11 (human) 0 0 0 0 0 0 (homologous ferret)
140	73	+ 0 0 0 0 0	++++(D) +++ +++ ++ +	++++(D) ++++(D) ++++(D) +++ ++	++++(D) ++++(D) ++++(D) ++++(D) ++++(D) ++++(D)	++++(D)×10 (human) 0 0 0 0 0 0 (homologous ferret)
258	76	+ 0 0 0 0 0				++++(D)×10 (human) 0 0 0 0 0 0 (homologous ferret)
672	82	0 0 0 0 0 0	+ + + 0 0 0	++++(D) ++++ +++ ++ ++ +	++++(D) −+++(D) ++++(D) −+++(D) ++++(D) ++++(D)	++++(D)×10 (human) 0 0 0 0 0 0 (homologous ferret)
16	50	++++(D) + ++ ++ ++ ++				++++(D)×8 (human) 0 0 0 0 0 (homologous ferret)
18	64	++++(D) + + ± 0				++++(D)×8 (human) 0 0 0 0 0 (homologous ferret)
16	86	++ + − + + 0				++++(D)×9 (human) ++ 0 0 0 0 0 (homologous ferret)
<9	65	+−+−(D) ++++(D) +++−(D) ++++(D) ++++(D)				++++(D)×6 (human) 0 0 0 0 0 0 (homologous ferret)

0–++++ degree of lung lesions (necropsy)
++++(D)×10, all 10 controls died within the period of the experiment

(D), mouse died within the period of the experiment.
Non-specific death is not recorded.

Antibody against Current Asiatic Strain Appearing after Vaccination with Monovalent Vaccines from Former Human A Strains

We had at our disposal 323 sera from people of different ages who had been vaccinated in 1956 and in the beginning of 1957 with monovalent vaccines of mouse-lines of former human A strains A/PR$_8$ (1934 U S A), A/FM$_1$ (1947 U S A), A/1951/Scandiv (1951 Ned), and A/1953 (1953 Ned)* Testing pre- and post-vaccination sera against the strain A/Asia/Japan/305/57 we found that a surprising number (9%) of the post-vaccination sera showed H I antibody against the Asiatic strain, even in the younger age-groups (table IV) These titres were again checked in duplicate on the same day A few M P tests done with pre- and post-vaccination sera again showed increases of true antibody against the current Asiatic strain in the post-vaccination samples The number of cases is too small to be analysed statistically in the different groups of people who received the different vaccines, but in every group increases of titre were found

Discussion

An outstanding finding is that the pattern of pre-epidemic Asiatic-influenza antibody in human sera shows a concentration in number and a rise in titre in people aged 71–94 Although the available number of sera in the age-group 0–30 was relatively small, it is very unlikely that, in this age-group, a similar antibody pattern would have been found as in the age-group 71 or more This phenomenon can therefore be compared with that demonstrated by Davenport et al (1953, 1955) and Hennessy et al (1955) of the appearance of high-titred H I antibody in people aged 35–38 (in 1953) against the dominant antigen of the influenza-A strain isolated from North American swine by Shope Fig 2 illustrates our confirmation of this work from a few sera investigated in the Netherlands

TABLE IV—POST-VACCINATION TITRES AGAINST INFLUENZA STRAIN A/ASIA/JAPAN/305/57 AFTER VACCINATION WITH FORMER HUMAN A STRAINS IN DIFFERENT AGE-GROUPS (MONOVALENT VACCINES)

Age-group (yr)	No vaccinated	No of positive H I titres	Height of post-vaccination H I titres[1]
1–9	8	0	
10–19	14	2	18–30*
20–29	42	2	16°–27
30–39	39	3	159*–23–18°
40–49	54	7	18–38–81–87–53–14–129*
50–59	92	7	408*–13–19–36–30–33–36
60–69	58	6	64–18–176*–14°–16–108*
70–79	15	2	24–20
80–85	1	0	
Total	323	29 (9%)	

1 All H I pre-vaccination titres of these cases were <9 Five positive pre-vaccination titres are omitted from this table and were incorporated in table I and fig 1

* Mouse-protection test positive

° Mouse-protection test doubtful

The first conclusion that can be drawn from fig 1 is that the human race most probably has been in contact with the dominant hæmagglutinating antigen of the current Asiatic strain in the last quarter of the 19th century, and that the 1957 pandemic of Asiatic influenza represented, in all probability, a repetition of an epidemic from that period

The analysis of antibody in human sera of different age-groups against the dominant antigen of the influenza-A swine strain indicates that the pandemic of 1918–19 was most probably the origin of the swine antibody in man, and that this pandemic was caused by the swine-influenza virus (Laidlaw 1935, Shope 1936, Davenport et al 1953) It remains, however, much less certain when the Asiatic-influenza antibody pattern shown in fig 1 originated, because most probably this figure shows only a poor remnant of a pattern which was much more extensive in number of positive titres and in height of titres shortly after the epidemic from which it was derived

There are some indications that the antibody pattern shown in fig 1 originated in the classic pandemic of 1889–90 The first high titres (140 and 258) against the current Asiatic antigen appear in the pattern in the ages 73 and 76, pointing to a possible origin about 1881–84 The greatest concentration of positive sera starts from the age of 76, again pointing to a possible origin around 1881 No important epidemic of influenza was registered in Europe between 1875 and 1889 Most workers (e g , Ripperger 1892, Leichtenstern 1896), with the exception of Hirsch (1881), do not consider the epidemic of 1875 to be a true pandemic, and most probably it did not originate in central Asia

If we assume that the pattern shown in fig 1 originated in the pandemic of 1889–90, an explanation should be sought for the fact that, in the age-group 70–76, only 5 positive H I titres were found in 161 examined sera (3 1%) A

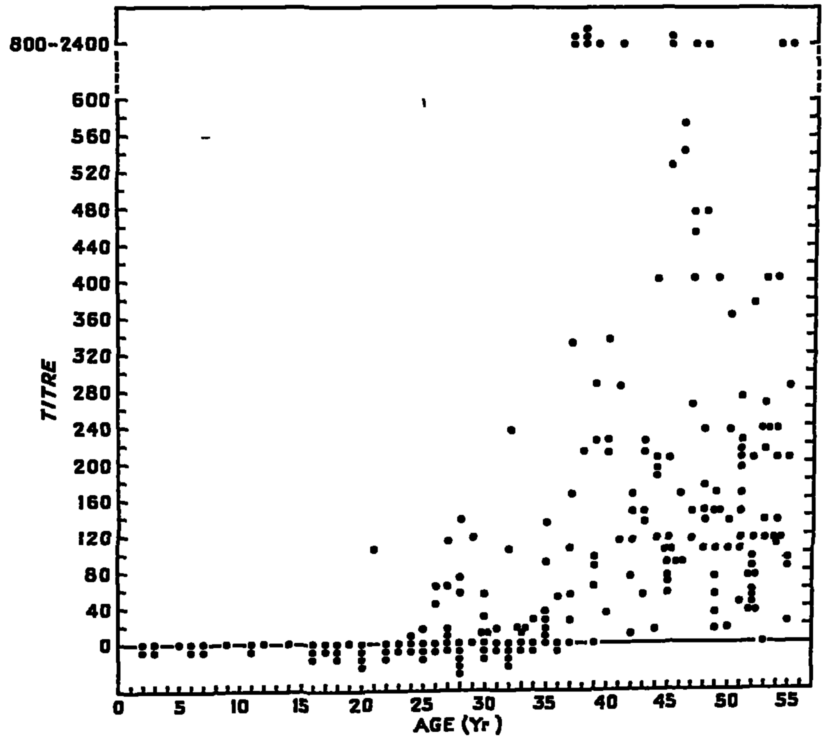

Fig 2—Age-distribution and H I antibody titres against influenza strain A/Swine/15 found in sera collected in Holland at beginning of 1957 (titres of <9 placed on or below zero line)

possible explanation may be that in the pandemic of 1889–90 school-children perhaps had a higher incidence of disease than had younger children, as was reported by several workers at that time (*Mitteilungen des Statistischen Amtes der Stadt München* 1891, Schmid 1895). Possibly other laboratories may supply more evidence of the presence of antibody in the age-group 70–76, because we must look on the pattern shown in fig. 1 as due largely to chance. The absence of a clear antibody pattern before the age of 70 is discussed below.

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* These vaccines were kindly produced at our request by the Biological Laboratories of N V Philips Roxane, Weesp

The 1890 origin of the antibody pattern shown in fig. 1 can also be explained on theoretical grounds. It is almost certain that the pandemic of influenza of 1889–90 originated in central Asia. The first cases were described by Heyfelder (1889) in May, 1889, in Bokhara, and the Russian doctors at that time called the disease "Chinese" influenza. Although Cantlie (1891) described an epidemic of febrile respiratory disease in September, 1888, in Hong Kong, thought by him to have been influenza, we cannot accept this diagnosis, because of the high incidence of skin rash in these patients and the appearance of jaundice in several cases.

The epidemiology of "true" pandemics of influenza differs sharply from that of the waves of seasonal influenza. True pandemics start in a certain part of the world, spread with the speed of human traffic irrespective of climatic and seasonal influences, and show a high morbidity, especially in people aged less than 40, and a relatively low mortality in their "first" wave.

Since the discovery of the human influenza virus (Smith et al. 1933) we know that interpandemic (seasonal) influenza virus A is continuously circulating in the world population, changing from time to time its antigenic make-up, probably selected by the antibodies built up against the dominant antigens of previous strains, and that, after a new dominant antigen is acquired, the precursor strain disappears rapidly.

In this respect it is most important to consider the fact that, from the work of Davenport et al. (1953) and from fig. 2, it can be concluded that, after 1918, the human race was in contact with the swine antigen for another 7–13 years. Since, in the cross-H.I. test, antigenic overlapping between the swine strain and the first isolated human influenza strain A/WS (1933 England) is clearly present, it is conceivable that, after 1918, derivatives of the swine strain were circulating, most probably with a different dominant antigen but with an antigenic relationship to swine. Strain analysis after 1933 has further shown that all the main human-strain types which appeared in 1934–56 were probably derived subsequently from a precursor. How far the dominant swine antigen can be "followed" in the strains appearing after 1933 has not yet been investigated carefully enough, and further experiments in this respect should be made in the future. Summarising, we can assume that, so far as the influenza-A group is concerned, the period 1918–56 may be considered as the "swine-influenza" era, even if the dominant swine antigen has vanished for the most part in the isolates found after 1933.

It is not improbable that we may accept the same course of events for the hypothetical influenza-virus of 1889, and that 1889–1918 represents an "Asiatic-influenza" era. Since hypothetical influenza-A strains circulating shortly before 1889 did not represent a "true" pandemic type, it is less probable that the 1957 Asiatic strain should be identical with such a strain, by chance starting a pandemic again in Asia, than to assume that a carriership of a particular A strain in Asia exists, presumably in an animal, causing human pandemics at long intervals of time. In this respect it is worth while to notice also that the "true" pandemics of 1830 and 1782 are considered to have originated in China (Ripperger 1892), and that strains of influenza virus isolated from North American swine in 1930–54 do not show great changes in antigenic composition (Gompels 1953, Jensen and Peterson 1957).

If fig. 1 represents a remnant of the antibody pattern originating in 1889–90, there is no definite evidence of the persistence of the "old" Asiatic antigen for a short period after 1890. It should be emphasised, however, that, if it had been present after 1890, the height of the titres would have been considerably lower than that of those originating in the pandemic itself (compare fig. 2), and that most probably the antibody would have vanished almost completely.

The hypothesis that the Asiatic strain of 1957, or a precursor strain with some antigenic relationship, has been in circulation for a long time, causing only scattered cases of influenza, seems improbable, because it would be very difficult to explain why such a strain should start a true pandemic again in Asia. The same can be argued against the theory that the Asiatic strain has been derived from recent human A strains by mutation.

For all those reasons we believe that the antibody pattern shown in fig. 1 may well have originated in the pandemic of influenza in 1889–90, and that the pandemic of Asiatic influenza in 1957 may have been a repetition of it, emerging from a pre-existing carriership in central Asia.

In the future it may be of importance to test again the present collection of old-age sera against new strains of influenza virus A which may turn up. If by chance the theoretical mutant of the current Asiatic virus which may appear in future should be found to be inhibited by human sera of a younger age-group than 70–100 (in 1957), almost certain proof of the identity of the current strain with that of 1889 could be obtained. At the same time it could be shown that the direction of the possibly developing mutation of the current Asiatic strain was the same as the one manifesting itself after 1890.

Difficult to explain are the facts in table IV. If the post-vaccination increases in H.I. titre against the Asiatic antigen were confined to the age-group 40 or more, they might indicate a stimulation of antibody against a remnant of the Asiatic dominant antigen present in derivative strains of the Asiatic type, which perhaps turned up in 1890–1918, after which the swine strain started to become dominant. This phenomenon is actually seen when people aged less than 20 are vaccinated with the strain A/PR$_8$ (1934 U.S.A.). In some cases post-vaccination titres against the swine strain appear, which can be explained by assuming a small antigenic overlapping of this strain with the PR$_8$ strain (Davenport and Hennessy 1956, Jensen and Peterson 1957, and our own unpublished observations). Since, however, the H.I. antibody against the Asiatic antigen after vaccination with heterologous recent human A strains appears also in persons born long after 1918, this theory cannot completely explain the phenomenon.

A possible explanation could be that there is still a minor overlapping in hæmagglutinating antigen between the Asiatic strain and recent A strains, which cannot be demonstrated with the routine animal antisera and methods used in the cross-H I test but may be shown by a highly sensitive antibody response of some people The possibility that a minor hæmagglutinating Asiatic antigen may be situated within the virus particle of previous A strains should also be kept in mind Meyer et al (1957) came to the same preliminary conclusion when they observed occasional small increases of titre against strains of the Asiatic type in their tests with paired sera from epidemics of previous years in military personnel as well as a few low H I titres against the same strains in sera from recruits vaccinated with a mixture of former A strains The occasional low H I titres found by us in persons aged less than 70 may be explained in the same way, although no-one was found associated with a positive C F test with soluble antigen or with a previous vaccination This observation emphasises the need for new experiments in which careful attention should be paid to minor overlapping titres between former A strains (including the swine strain) and the Asiatic type The use of high-titred animal antisera produced with adjuvant vaccines might perhaps be helpful in these tests

Summary

Pre-epidemic antibody against the 1957 Asiatic influenza virus was found in greatest number and with highest titre in people aged 71 or more living in the Netherlands

This suggests that the 1957 pandemic of influenza was a repetition of an epidemic which appeared in the last quarter of the 19th century, and that this epidemic might well have been the pandemic of 1889–90, which also originated in Asia

Similar investigation in the future of a possible mutant of the current Asiatic virus might be of importance to substantiate this theory

Low increases of antibody titre against the current Asiatic strains were observed in some people in younger and older age-groups after vaccination with monovalent vaccines from former human A strains

To explain this phenomenon a careful study of eventually existing minor overlapping of hæmagglutinating antigen between the Asiatic strain, former human A strains, and the strain of swine influenza may be helpful

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SEROLOGICAL STUDIES WITH ASIAN STRAIN OF INFLUENZA A

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WHEN the virus of Asian influenza was isolated in Singapore in May, 1957, it was found to be an influenza-A strain because it contained the soluble complement-fixing antigen common to all influenza-A strains It differed from all previous influenza-A strains, however, in that the hæmagglutination-inhibition test, which detects strain-specific antigens, showed no cross-reactions with any previous strain (Jensen 1957, Meyer et al 1957) This explains the finding that only a very small proportion of people before exposure to the virus had hæmagglutination-inhibiting antibodies against the Asian strain (Meyer et al 1957, Davoli and Corsi 1957, J Mulder, personal communication)

This absence of antibodies in the pre-epidemic sera gave a wonderful opportunity for studying the effect of the epidemic of Asian influenza on the serological status of the population It was first necessary to establish the effect of clinical illness due to the virus on the antibodies demonstrated by the hæmagglutination test This was done by testing pairs of sera from some patients in various school and other epidemics and from others admitted to hospital with pneumonia and other complications of influenza A group of university students were also bled five weeks after the epidemic, and the findings were compared with the histories in these persons of illnesses resembling influenza

Population studies were made by hæmagglutination tests on random sera collected before the outbreak between 1955 and 1957, some of which were pooled by age-group, and on individual and other pooled sera collected in November, 1957, two months after the peak of the epidemic Sera from patients with influenza in 1949, 1951, and 1956 and from persons inoculated with various influenza-virus vaccines in 1955 and 1956 were also tested by the same methods in the hope of throwing light on the relationship between the Asian-virus antigen and those appropriate to earlier influenza-A viruses

Materials and Methods

Sera were kept at –26°C for periods of a few weeks to 2 years, except for those collected in 1949 and 1951, which were freeze-dried.

Viruses—The strains of influenza virus used were FM1 1947, A/England/1/51, A/England/211/56 (all representative of past A strains and referred to later as A prime strains), and A/Singapore/1/57 Pools of virus for hæmagglutination-inhibition tests were made by intra-allantoic inoculation of 10-day embryonated eggs with a dilute suspension of virus After 48 hours' incubation at 35°C the allantoic fluids were harvested, pooled, and stored at –26°C in small bottles

Hæmagglutination-inhibition (H I) *tests* were made by a modification of the World Health Organisation's (1953) plastic-plate technique

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*In receipt of a grant from the Medical Research Council

Phosphate-buffered saline solution (pH 7 2) was used instead of physiological saline solution and all the sera were treated overnight with cholera filtrate The method of preparing the cholera filtrate and that of treating the sera were as described by Hilleman and Werner (1953) This treatment was necessary because influenza A/Singapore/57 is very susceptible to non-specific inhibitor In all the experiments, except those on pooled sera and vaccination sera, red cells were obtained from the same fowl The titre of a serum was expressed as the reciprocal of the initial dilution producing partial inhibition

Complement-fixation tests —A modification of the method of Fulton and Dumbell (1949) was used, influenza-A soluble antigen being prepared from the chorio-allantoic membrane of eggs infected with the WS strain The methods used have been described previously (Balducci et al 1956)

Results

Serological Tests on Pairs of Sera from Patients with Influenza in the 1957 Epidemic

Both H I tests against A/Singapore/57 and complement-fixation tests using an influenza-A soluble antigen were done on 80 pairs of sera from patients with influenza They included sera from patients in two public schools, an R A F station, the university health service, and employees at a steel works The remainder (31) were from patients with influenza admitted to hospital mainly with complications—e g, pneumonia

Influenza-A virus of Asian type was isolated in eggs from three of these patients and from four of their contacts

Table I shows the results of the H I tests on these sera It will be seen that most of the acute specimens of serum from uncomplicated cases of influenza contained no detectable hæmagglutination-inhibiting antibody The acute specimen of serum was often collected rather late in the illness from the patients admitted to hospital, and antibody was detected in two-thirds of these sera

TABLE I—HÆMAGGLUTINATION-INHIBITION TITRES OF PAIRS OF SERA FROM CLINICAL CASES OF INFLUENZA

Category	Phase of illness	No of sera	Distribution of H I titres							Cases with rises of antibody
			< 10	10–15	20–30	40–60	80–120	160–240	> 240	
Uncomplicated influenza	Acute	49	46	3						27 (55%)
	Convalescent	49	19	9	6	7	7		1	
Admitted to hospital	Acute	31	10	5	8	4	2	1	1	21 (68%)
	Convalescent	31	5	1	5	1	4	5	10	

The convalescent sera contained antibody in 30 of the uncomplicated cases (61%) and in 26 (84%) of the hospital patients Fourfold or greater increases of antibody were detected by the H I test in 27 (55%) of uncomplicated cases and in 21 (68%) of the hospital patients

The results of the complement-fixation tests were similar Most of the acute specimens of serum gave titres of less than 4 Complement-fixing antibody was present in the convalescent serum of 84% of uncomplicated cases and 74% of the hospital patients Fourfold or greater increases of antibody were detected by the complement-fixation test in 36 (74%) of uncomplicated cases and in 18 (58%) of the hospital patients Thus in the uncomplicated cases the complement-fixation test was positive more often than the H I test.

13% of the patients showed no significant level of antibody in the convalescent serum by either test, a further 7% developed antibody detected only by the H I test, and 19% showed complement-fixing antibody only

From these results it is possible to guess that about 30% of the population of Sheffield who had attacks regarded as clinical influenza had no antibody detected by the H I test in their sera during convalescence

TABLE II—HÆMAGGLUTINATION-INHIBITION TESTS ON SERA FROM MEDICAL STUDENTS

History of clinical influenza	No positive	No negative	Total
Yes	17	3	20
Doubtful	2	1	3
No	5	19	24
Total	24	23	47

Sera with titres of 10 or more were considered positive.

Relationship between Positive Hæmagglutination-inhibition Test and History of Clinical Influenza

In the third week of November, 1957, five weeks after the peak of the outbreak in the university students, single samples of serum were collected from 47 first-year students At the same time they were asked whether or not they had had illnesses resembling clinical influenza The results of H I tests against A/Singapore/57 on these sera are shown in table II There was good correlation between a history of influenza and a positive H I test

The results showed that 5 (about 20%) of infections producing hæmagglutination-inhibiting antibody were subclinical Probably at least the same proportion of all infections, both with and without detectable serological response, were subclinical The results cited above showed that about 30% of all patients with presumed influenza had no detectable hæmagglutination-inhibiting antibody in their convalescent sera The figures for the above-mentioned students (4 of 23) are comparable with these Thus the H I test done on a single specimen of serum would detect only 70% of recent cases of clinical influenza but would reveal a further 20% with subclinical infections

Comparison of Antibodies in Population before and after the Asian Influenza Epidemic

Tests were done to study the effect of the 1957 epidemic on hæmagglutination-inhibiting antibodies to Asian virus in the population of Sheffield and neighbourhood It was hoped that information would be obtained about the extent of infection in the population during the epidemic

Pre-epidemic sera —Table III shows the results of the H I tests against A/Singapore/57 on 154 sera collected in England before July, 1957 Most of these sera had come from the north of England from suspected cases of toxoplasmosis, 39 were from suspected cases of virus infection from Sheffield, and 19 were from persons aged 80 or more in an old people's home

TABLE III—RESULTS OF HÆMAGGLUTINATION-INHIBITION TESTS AGAINST A/SINGAPORE/57 ON SERA COLLECTED BEFORE THE EPIDEMIC

Age (yr)	No tested	No with titres of 10 or more	Titres
0–9	23	1	80
10–19	21	0	
20–29	28	1	20
30–39	27	2	10 & 30
40–49	10	0	
50–59	13	0	
60–69	11	1	30
70–79	2	0	
80–89	18	1	80
90–92	1	0	
Total	154	6	

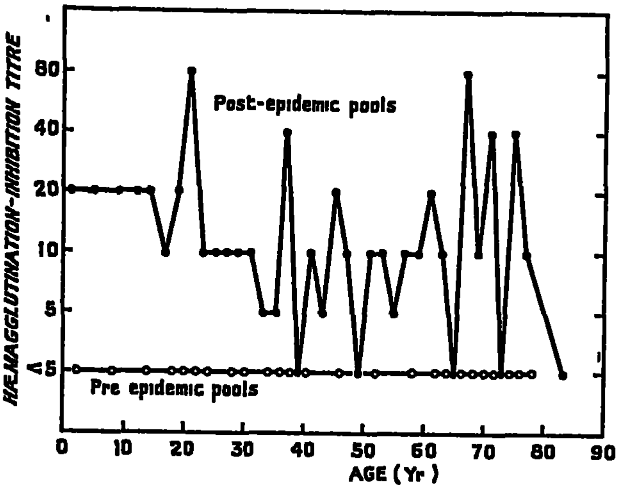

Fig. 1—Titres of pools of sera tested against A/Singapore/57.

6 of the sera gave titres of 10 or more. They were from persons of various ages, and only one of these belonged to the old-age group. In repeat experiments the numbers of such sera varied with the batch of cholera filtrate used, and in one experiment, in which a particularly weak batch was used, 25 sera gave positive results. Neutralisation tests were not done, so it was impossible to decide whether the six sera actually contained antibody against the Asian strain or whether the result was due to non-specific inhibitor. In addition to these, none of the sera taken from the 168 persons before vaccination in 1955 and 1956 (see below) contained inhibitor against the Asian strain. These people were mostly young adults.

Besides these individual sera, pools of sera collected in 1955 were tested by hæmagglutination-inhibition against A/Singapore/57. The sera had been pooled according to age in two-year age-groups, up to 50 sera being put into each pool. 25 of the pools between the age of 2 and 78 were tested (fig. 1), and all had titres of less than 5. This was very different from the results obtained with similar serum pools collected in 1954 in Sheffield and tested against other viruses (Davenport et al. 1955). It thus appears that most of the sera from the population of Sheffield were devoid of detectable antibody against the Asian strain before the outbreak.

Post-epidemic sera.—The peak of the epidemic in Sheffield was during the week ending Sept. 21, 1957. Between Nov. 1 and Nov. 30, 1957, 1660 sera were collected by the Sheffield Blood Transfusion Service, the Sheffield Public Health Laboratory, and the pathological laboratories of many of the Sheffield hospitals. Most of them came from blood-donors or were sent for Wassermann tests, the rest being sent to the laboratories for various routine tests. All these sera were tested after pooling according to age, and many were also tested individually.

637 sera were tested individually against the A/Singapore/57 virus (fig. 2). 283 (44%) had titres of 10 or more. The percentage of sera positive in each 10-year age-group was 16–71%, being highest under the age of 20 and lowest between the ages of 60 and 69. This variation may reflect the attack-rate in the different age-groups but may also have been partly due to the fact that different pools of antigen were used in the various tests.

All the 1660 sera (including those tested individually) were pooled according to age as follows: (1) between the ages of 17 and 76 they were pooled in 2-year age-groups, (2) the age ranges of the remaining pools were 0–3, 4–7, 8–11, 12–13, 14–16, 77–79, and 80–88, and (3) each pool consisted of 50 sera, except those from persons aged less than 16 and persons aged more than 66, which contained 21–47 sera.

All the pools were tested by hæmagglutination-inhibition against A/Singapore/57 at the same time that the 1955 pools were tested. Thus in one experiment, using the same antigen, red cells, and cholera filtrate, the age-distribution of antibody against the Asian virus was determined in 1660 post-epidemic sera. The results are shown in fig. 1. There was considerable variation from pool to pool, and there was no obvious trend with age. But there was a remarkable difference in the results of the tests against A/Singapore/57 virus with the sera collected before and after the epidemic.

Cross-hæmagglutination-inhibition Tests

With sera from cases of influenza.—Table IV shows the results of tests on acute and convalescent specimens of serum from patients with influenza in 1949, 1951, 1956, and 1957. None of the sera collected before 1957 showed rises in inhibition titre against A/Singapore/57, although

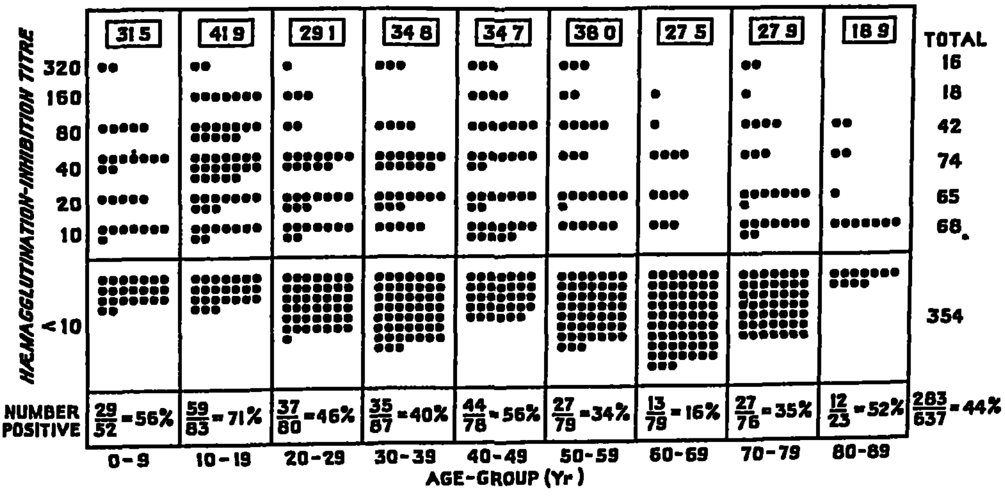

Fig. 2—Post-epidemic sera tested against A/Singapore/57. Numerals in rectangles denote geometric means of sera with titres of 10 or more.

TABLE IV—TESTS ON PAIRED SERA FROM PATIENTS WITH INFLUENZA IN 1949, 1951, 1956, AND 1957

Case no	Titres in complement-fixation test v soluble antigen	Hæmagglutination-inhibition titres against			
		FM1	A/Eng /51	A/Eng /56	A/Sing /57
1949					
1	0/8	0/30			0/0
2	0/>64	0/120			0/0
3	16/>64	0/240			0/0
1951					
1	0/48		0/30		0/0
2	0/32		0/7·5		0/0
1956					
1	0/16			0/15	0/0
2	0/24			0/30	0/0
3	0/8			0/7·5	0/0
4	0/>64			0/160	0/0
5	0/16			0/7·5	0/0
6	8/32			0/15	0/0
1957					
1	0/8			0/0	0/30
2	0/>64			0/0	10/>320
3	0/6			0/0	0/30
4	0/64			30/20	0/15
5	6/8		60/20	15/<10	0/30
6	0/24		15/30	0/15	0/80
7	0/48		10/10	7·5/7·5	0/15
8	0/48		10/10	<10/0	0/30
9	0/24		80/60	7·5/7·5	0/15
10	6/>64		0/60	7·5/60	0/120
11	0/48		60/60	120/120	0/120

0 less than 4 in the complement-fixation tests and less than 5 in the hæmagglutination-inhibition tests

all showed rises in titre against the strains prevalent at the time of collection. Most of them were from young adults 11 pairs of sera from patients with influenza in the 1957 epidemic which showed rises in titre against A/Singapore/57 were tested against A/England/51 and A/England/56 Whereas some of these sera contained antibody against these "A prime" strains, in only 2 cases was there a rise in titre. This shows that anamnestic reactions, such as occur between influenza-"A prime" and influenza-A strains (Stuart-Harris and Miller 1947), can also occur between the Asian virus and "A prime" strains

With sera from vaccinated persons—H I tests against A/Singapore/57 were done on 168 pairs of sera from people vaccinated with one dose of influenza vaccine in 1955 and 1956 The first specimen was taken before vaccination and the second about four weeks after For those given oil adjuvant vaccines a third specimen was taken three months after vaccination. 32 persons were given a monovalent vaccine containing A/England/54, 15 a monovalent vaccine containing A/Malaya/54, 14 a monovalent vaccine containing A/England/55, 42 a monovalent oil adjuvant vaccine containing A/England/56, and 65 a polyvalent vaccine containing swine, PR8, and FM1 influenza-A viruses Most of the subjects were aged 18–25, but 7 given the polyvalent vaccine, 7 given the A/England/54 vaccine, and an unknown number given the A/England/56 vaccine were aged more than 25 Most of the 168 sets of sera had shown rises in titre by the H I test against the homologous antigen

The H I titres of pre- and post-vaccination specimens from 160 of the vaccinated persons were less than 10 In the remaining 8 sets of sera (5%) the titres of the first specimen were less than 10 and those of the second or third were 15 (4 instances), 20, 30, and 40 (2 instances) 4 of these titres were confirmed on repetition 2 of the sera were from persons given the polyvalent vaccine and 6 the A/England/56 monovalent vaccine.

It thus appears that inhibitor against the Asian-virus antigen was occasionally stimulated to appear in the serum after immunisation with a single injection of vaccine made from an influenza virus recovered before 1957 Our inability to detect similar appearances of inhibitor after infection with the latter viruses may have been due to the small number of available sera tested Meyer et al (1957) detected inhibitor to the Asian virus in sera from some patients with clinical influenza before the Asian epidemic. Such naturally developing antibody would explain our own finding of occasional inhibitor to the Asian virus antigen in the pre-epidemic sera

Discussion

The serological results obtained in Sheffield in cases of Asian influenza are similar to those found during previous epidemics of influenza A and are in conformity with the results of other workers The H I test using the Singapore virus showed a rise of antibody in 60% and the complement-fixation test in 68% of cases The corresponding results obtained during the 1951 epidemic were that H I tests with the appropriate virus antigen were positive in 59% and complement-fixation tests using soluble antigen were positive in 75% of cases (Stuart-Harris 1953) During the Asian epidemic the H I test detected antibody in convalescence in 70% of clinical illnesses but also indicated subclinical infection in 20% of the population Lim et al (1957) found in Singapore that the H.I test detected antibody in 67% of patients with Asian influenza admitted to hospital and revealed subclinical infection in 13% of persons who remained symptom-free

The study of the distribution in the population of Sheffield of antibody detected by the H I test after the epidemic showed that at least 16–71% of persons of various ages had become infected Even 30–50% of those aged 70 or more showed evidence of infection The appearance of antibody in a high proportion of young adults and children agreed well with the numbers of illnesses observed by practitioners However, many doctors in Sheffield commented that there were relatively fewer illnesses in those aged more than 40, and the attack-rate in Beckenham measured by Fry (1958) fell progressively after the age of 20 It seems likely that many infections in the older persons in Sheffield were either very mild or asymptomatic. The average attack-rate in the population which could be surmised from these serological results was at least 50%

The geometric mean titres of antibodies found at various ages in the post-epidemic period, if we ignore the sera which did not inhibit agglutination at 1 in 10 dilution, showed relatively little variation with age (fig 1) The highest mean titre was in the second decade, and that in persons aged more than 60 was not so high This appeared to indicate a relatively uniform serological response to infection such as would be expected if the Asian-virus antigen had not been experienced previously by those who became ill

The finding of inhibitor to the Asian virus in 6 of 322 sera collected before the epidemic has to be considered in association with the observed appearance of inhibitor in 8 of 168 persons immunised with various influenza-virus vaccines which did not contain Asian virus We have no proof that the inhibitor was neutralising antibody, but the assumption that this was so is reasonable. These instances of serum inhibition were infrequent and bore no apparent relation to age. Mulder (1957) has brought forward evidence that antibody to the Asian virus was

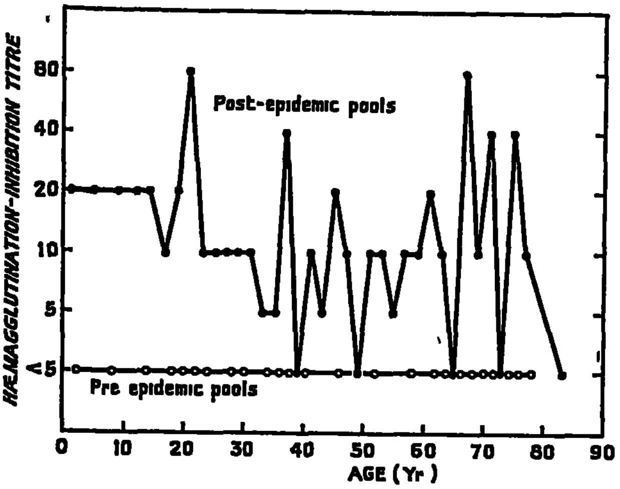

Fig 1—Titres of pools of sera tested against A/Singapore/57

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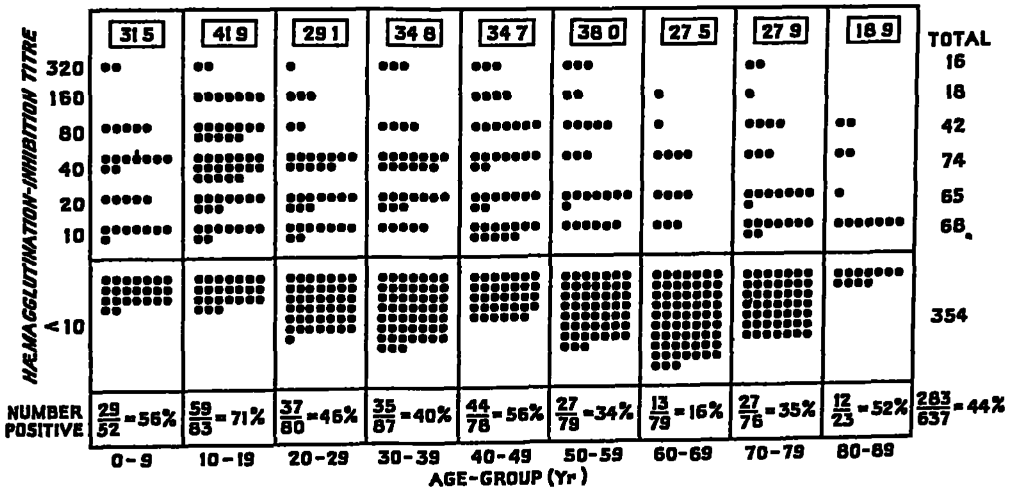

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6	0/24		15/30	0/15	0/80
7	0/48		10/10	7 5/7 5	0/15
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The serological results obtained in Sheffield in cases of Asian influenza are similar to those found during previous epidemics of influenza A and are in conformity with the results of other workers The H I test using the Singapore virus showed a rise of antibody in 60% and the complement-fixation test in 68% of cases The corresponding results obtained during the 1951 epidemic were that H I tests with the appropriate virus antigen were positive in 59% and complement-fixation tests using soluble antigen were positive in 75% of cases (Stuart-Harris 1953) During the Asian epidemic the H I test detected antibody in convalescence in 70% of clinical illnesses but also indicated subclinical infection in 20% of the population Lim et al (1957) found in Singapore that the H I test detected antibody in 67% of patients with Asian influenza admitted to hospital and revealed subclinical infection in 13% of persons who remained symptom-free

The study of the distribution in the population of Sheffield of antibody detected by the H I test after the epidemic showed that at least 16–71% of persons of various ages had become infected Even 30–50% of those aged 70 or more showed evidence of infection The appearance of antibody in a high proportion of young adults and children agreed well with the numbers of illnesses observed by practitioners However, many doctors in Sheffield commented that there were relatively fewer illnesses in those aged more than 40, and the attack-rate in Beckenham measured by Fry (1958) fell progressively after the age of 20 It seems likely that many infections in the older persons in Sheffield were either very mild or asymptomatic The average attack-rate in the population which could be surmised from these serological results was at least 50%

The geometric mean titres of antibodies found at various ages in the post-epidemic period, if we ignore the sera which did not inhibit agglutination at 1 in 10 dilution, showed relatively little variation with age (fig 1) The highest mean titre was in the second decade, and that in persons aged more than 60 was not so high This appeared to indicate a relatively uniform serological response to infection such as would be expected if the Asian-virus antigen had not been experienced previously by those who became ill

The finding of inhibitor to the Asian virus in 6 of 322 sera collected before the epidemic has to be considered in association with the observed appearance of inhibitor in 8 of 168 persons immunised with various influenza-virus vaccines which did not contain Asian virus We have no proof that the inhibitor was neutralising antibody, but the assumption that this was so is reasonable These instances of serum inhibition were infrequent and bore no apparent relation to age Mulder (1957) has brought forward evidence that antibody to the Asian virus was present in Holland in some aged persons before the epidemic and was rare in persons aged less than 80 He also observed (personal communication) the development of antibody after immunisation with an influenza vaccine which did not contain the Asian strain Our own results do not entirely conform with Mulder's view that the Asian virus is essentially the virus responsible for the 1890 pandemic An alternative explanation is that the Asian virus shares a minor antigenic component with some of the influenza viruses experienced before 1957 This minor component might represent the survival of a major antigen from some virus causing a human pandemic in the past It could form the basis for a genetic variation in which the minor component had become the major antigen recognised in 1957 as that of the Asian virus

Summary

H I antibody to the Asian influenza-virus antigen was detected in 70% and complement-fixing antibody to the soluble A antigen in 80% of convalescent sera from 80 cases of influenza with or without complications in Sheffield during the 1957 epidemic of Asian influenza

In 47 students H I tests on sera taken after the epidemic showed that 20% of infections were asymptomatic

6 of 322 sera collected before the epidemic contained inhibitor to the Asian virus 283 (44%) of 637 sera collected after the epidemic in Sheffield contained inhibitor, the number varying between 16% and 71% in persons of different ages

Pools of sera collected before 1957 and assembled by age showed no H I antibody to the Asian virus Similar pools of sera collected after the epidemic showed antibody in amounts varying within wide limits Probably at least half the population had been infected during the epidemic

H I antibody against the Asian virus appeared in the serum of 8 of 168 persons vaccinated with " A prime " and polyvalent vaccines but was not detected in the convalescent sera from 11 patients with influenza before 1957

The significance of the results is discussed in regard to the relationship between the Asian and other influenza-A viruses

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STRAIN-SPECIFIC COMPLEMENT-FIXATION TEST IN ANTIGENIC ANALYSIS AND SERODIAGNOSIS OF INFLUENZA *

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Difficulties have arisen in the use of the hæmagglutination-inhibition test for antigenic analyses of strains of influenza virus by specific immune sera and for strain-specific serodiagnosis

Uncertainty in the interpretation of the results has been introduced by (1) phase variations in the viruses, on adaptation to laboratory hosts, as regards the degree of agglutination or the species of red cells agglutinated, and (2) differential susceptibilities of strains to one or more of the non-specific inhibitors present in immune sera derived from different animals Though several techniques are used for removing inhibitors from sera, none is universally successful, and there is no assurance that specific antibody levels remain unaffected For these reasons other methods of determining antigenic patterns and strain-specific antibody responses were sought

The complement-fixation test (C F T) is highly satisfactory for these purposes so long as the type-specific soluble antigen (S) common to all strains of one type and the strain-specific virus antigen (V) are clearly separated Equally essential is the use of anti-S sera free from anti-V (for proving absence of S in V) and, conversely, of anti-V sera devoid of antibodies to S These requirements have not generally been met in the past, but these reagents can now be produced regularly The non-specific inhibitors of hæmagglutination do not interfere with the C F T

Methods

The *S-antigen* is obtained by exposing virus particles to ether (Hoyle 1952, Lief and Henle 1956a) The internal S thus released is freed from all V by exhaustive adsorption on to chicken and guineapig red cells

Anti-S sera are produced by intranasal inoculation of guineapigs with small doses of active virus, followed after five or more weeks (when initially formed anti-V has disappeared) by an intraperitoneal injection of S prepared from a distantly related homotypic strain Thus only anti-S is boostered (Lief et al 1958)

Virus particles separated from infected allantoic fluids by two cycles of adsorption on to and elution from red cells are suitable as *V antigens* for C F T , since such suspensions are usually free from external S (Lief and Henle 1956b)

Guineapig *anti-V sera* are produced by three or more intraperitoneal injections of the hæmagglutinin fraction (devoid of external and internal S) obtained from ether-treated elementary bodies by the red-cell adsorption-elution procedure (A Fabiyi, F S Lief, and W Henle, unpublished)

Results

Cross-matching of V antigens of 36 type-A strains, isolated between 1931 (swine influenza S-15 strain) and 1957 (A-Japan-305), with the corresponding anti-V sera in block titrations revealed antigenic patterns in general

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TABLE I—ANTI-V RESPONSES IN SELECTED PATIENTS OF A_1 AND ASIAN INFLUENZA

Case no	Age (yr)	Virus	Days after onset	Serum titres v antigens								
				S-15–V 1931	PR8–V 1934	F_{99}–V 1940	L_1–V 1947	Phila.–V 1953	NL_1–V 1957	Asian–V 1957	S type A	Lee–V type B
1	10	NL_1	8/22	8/16	8/32	0/4	32 64	32/128	32/256	0/4	0/32	0/0
2	13	,,	3/17	0/16	0/32	0 8	0/128	8/128	0/128	0 4	8/96	0/0
3	13	,,	–/15	–/32	–/32	–/16	–/128	–/128	–/128	–/16	–/128	–/8
4	16	,,	4/18	0/32	8/64	0/24	8/128	8/128	0/128	-0 8	32/256	0/0
5	39	,,	2/16	8/64	0/32	8/24	0/32	0 64	0 64	0/128	8/64	0 0
6	47	,,	2/16	32/64	16/64	8/32	8/48	8/48	0/32	0/64	12/64	16/16
7	52	,,	1/15	12/64	8/128	0/64	8/128	0/256	0/256	4/12	8/256	0/0
8	1	Asian	1/8	0/4	0 0	0/4	0/0	0 0	0 0	4 96	0/48	0/0
9	1½	,,	3/24	0/192	0/24	0/24	4/192	8/128	16/256	8/256	4/128	0/0
10	4	,,	3/17	0 24	0/12	0/24	0 48	8/48	8/128	0/128	0 64	0/0
11	63	,,	9/19	16/32	0 0	0 0	16/4	0 0	0/0	6/256	6/256	0/0
12	77	,,	4/39	0 96	0/0	0/48	0/64	0 48	0/96	0/128	0 96	0/0
13	84	,,	1/15	0/32	0 0	0 24	4/32	4/48	4 96	0/96	0/32	0/0
Anti-S (type A)				0	0	0	0	0	0	0	*256	0

* 0 = <1 4

agreement with those obtained in other laboratories by hæmagglutination-inhibition methods (Hirst 1952, Hilleman 1951, Jensen and Francis 1953) The anti-Asian V serum (A-Japan-305) reacted to some extent with WS (1933) V, and anti-V sera to a 1951 and 1953 strain fixed complement to low titres in the presence of Asian V Such " one-way cross-reactions ", seen also in other combinations and often extending over several type-A families of strains, may reflect differences in the in-vitro and in-vivo antigenicity of some components

The strain-specific anti-V sera were effective in the rapid identification of new isolates of virus during outbreaks of A¹ and Asian influenza in 1957 In most cases the identity and antigenic relationships were established with first chick embryo-passage materials, so long as the amniotic or the allantoic fluids contained more than 20 hæmagglutination units per ml (F S Lief, M Ostapiak, A Fabiyi, and W Henle unpublished) Rarely three chick embryo passages were required before these determinations were feasible.

The V antigens were found suitable for strain-specific serodiagnosis of influenza (F S Lief and W Henle, unpublished) More than 90% of more than 800 cases of Asian influenza revealed significant increases in antibodies to the specific V antigen An increase in type-specific anti-S was noted in all cases except those in very young children In most instances it preceded development of anti-Asian V because, most likely, it represented usually a recall Absence of anti-V responses was referable to premature collection of convalescent blood

The anti-V responses during the Asian influenza epidemic and the preceding A¹ outbreak were rarely restricted to the infecting viruses, if they were, it was mainly in very young patients The spectrum of these responses was by no means limited to strains circulating during the life-span of the individual Table I presents the serological data in a few selected cases None of the patients had anti-V to the infecting strains in the acute-phase sera, so long as the samples of sera were taken in the first few days of illness, but all the convalescent sera were positive Reactions with other V antigens in the acute-phase sera reflected to some extent the patient's age, in that positive results with early strains, such as S-15 and PR8, were noted mainly in older age-groups, but there were exceptions—e g , cases 1 and 4 Yet in the convalescent sera responses were observed in many cases to V-antigens prevalent before the patient's birth In a considerable number of the A¹ infections (about 35%) in addition antibodies developed to Asian V before this agent appeared These reactions showed no apparent relation to the patient's age Such responses were recorded previously in A¹ patients (Meyer et al 1957) and persons immunised with pre-Asian influenza vaccines (Mulder and Masurel 1958)

The results obtained with the acute-phase sera appear to be in agreement with those of previous antibody surveys using hæmagglutination-inhibition tests (Mulder and Masurel 1958, Davenport et al 1953, Hennessy et al 1955) in that, with increasing age, antibodies to progressively earlier strains were found This has been interpreted to mean that the virus responsible for the initial influenza in childhood determines the antibody responses to subsequent exposures to antigenically different strains and, with it, the antibody patterns found throughout life If this interpretation is correct, the results suggest that the pandemic of 1918–19 was caused by a strain of what is now known as swine influenza virus (Shope 1936), and that of 1888–89 by an agent closely related to Asian influenza virus (Mulder and Masurel 1958), but the fact that some relatively young patients responded with antibodies to the S-15, PR8, and Japan-305 strains cannot be overlooked The development of anti-V in a patient to strains to which he could not possibly have been previously exposed suggests other interpretations

A broadening of antibody responses in animals after

TABLE II—ANTI-V RESPONSES IN GUINEAPIGS AFTER SUCCESSIVE INFECTIONS WITH DIFFERENT STRAINS OF INFLUENZA-A VIRUS

Exposure		Weeks after start	Serum titres v antigens								
Case no	Strain		S-15-V 1931	PR8-V 1934	F_{99}-V 1940	L_1-V 1947	Phila.-V 1953	NL_1-V 1957	Asian-V 1957	S type A	Lee-V type B
1	S-15	0/3	0/128*	0 0	0/16	0 0	0 0			0/128	0/0
2	PR8	21/24	0/256	0 256	0 256	0 128	0 64			0/512	0 0
3	F_{99}	36 39	128/256	64 64	64 192	24 48	0/12			128/192	0/0
4	L_1	49/53	128/128	64/128	64/128	24/128	12/16	0/32	0/48	128/128	0/0
1	PR8	0/3	0 0	0 64	0 0	0 0	0 0			0 64	0 0
2	F_{99}	10 13	0/0	32 64	8/64	0/32	0 0			0 128	0 0
3	L_1	26 30	0 8	32/256	32/128	12 256	0/32	0 16	0 12	64/128	0 0
Anti-S (type A)		—	0	0	0	0	0	0	0	256	0

* Serum titre at time of exposure/titre 3–4 weeks later

repeated infections or intraperitoneal injections of active virus has been observed in early studies (see Van Rooyen and Rhodes 1948) This problem was reinvestigated by repeated intranasal inoculations of guineapigs at intervals of ten to twenty-one weeks with active influenza viruses of progressively later vintage or even with the same strain

The first exposure usually induced strain-specific anti-V responses—i e , to the homologous and closely related strains

On second and subsequent exposures these antibodies were recalled and, *in addition, whether the same or different viruses* were used for reinoculations, the antibody spectra rapidly broadened The examples offered in table II revealed that ultimately antibodies were formed to V antigens which were not detectably represented in the infecting strains, including Asian V

It was noted also that, after second or third exposures, the ensuing antibody levels declined at slower rates than after the first infection

The anti-V reactions observed at the time of the third or fourth exposures were not restricted to the viruses used for previous inoculations

Discussion

These results indicate that influenza strains contain a multiplicity of antigens The dominant, and possibly also the minor, directly detectable components determine the antibody responses on primary infection (Jensen and Francis 1953) Recall of these antibodies on subsequent exposures to different type-A viruses, as well as the anti-V responses to antigens not measurable in the infecting agents, suggests that most, if not all, of the various antigenic components are present mainly at submeasurable levels in any of the strains Because of the low concentration of most of the antigens several exposures are required before many of the antibodies appear in the serum

If these observations apply to man, the presence of *antibodies to a wide spectrum of* V *antigens may reflect* in part the multiplicity, and possibly spacing and severity, of previous exposures, and not only the antigenic structure of the virus responsible for the primary infection The older the person, the more influenza infections he is likely to have experienced in the past The presence of antibodies to swine or Asian influenza viruses in the older age-groups does not necessarily denote, therefore, that they had been infected with these specific agents at the time of the agents' prevalence Multiple infections with other strains at later dates also could have ultimately produced these antibodies This problem may be resolved in the future, depending on whether the age-distribution of antibodies to early strains will remain unchanged in ten or more years, or whether anti-S-15 or anti-PR8 reactions will be found gradually in higher age-groups

It remains to be shown that the various anti-V reactions recorded reflect immunity If so, present immunisation procedures for man deserve reconsideration It has been observed that guineapigs, after as many as six intraperitoneal injections of non-infectious hæmagglutinin fractions, still yield strain-specific sera, whereas, as shown above, a few intranasal instillations of active virus induce broad responses, covering antigens not only of past but also subsequent prevalence

Summary

A new technique is described for the antigenic analysis of influenza viruses and serological diagnosis of influenza The method, a strain-specific complement-fixation test with the V (or viral) antigen, avoids the problems of nonspecific inhibitors and antibody-virus avidity which make the interpretation of the hæmagglutination-inhibition test so difficult

By means of this technique it was possible to type Asian viruses rapidly and to achieve a positive serological diagnosis in more than 90% of 800 paired sera The antibody responses, however, were rarely restricted to the infecting strain, and were in many cases broad enough to cover strains prevalent before the birth of the patients

Experimentally, it was found that guineapigs infected repeatedly with the same strain or with strains of progressively later vintage gradually developed a broadening antibody response which embraced strains not included in the infecting strains—e g , the Asian strain

It is concluded that antibody to Asian virus does not necessarily denote infection with that particular strain at the time when this virus was prevalent but could be produced by multiple infection with other strains at later dates

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A SEROLOGICAL TRIAL OF ASIAN-INFLUENZA VACCINE AFTER THE AUTUMN EPIDEMIC*

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SEROLOGICAL trials of an influenza vaccine prepared from the Asian strain before the epidemic, showed, in contrast to previous experience (Beveridge 1944), that two doses were needed for a good serological response (Medical Research Council 1958, Commission on Influenza 1957) A further trial was therefore arranged in November, after the epidemic, by the Directorate of Hygiene and Research of the Royal Air Force at the request of the Medical Research Council's Committee on Influenza and other Respiratory Virus Vaccines

The object of this trial was to determine the serological response to one and two inoculations of the above vaccine in volunteers who had been exposed, but *not ill*, and in those who had had influenza in the autumn epidemic

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* A report to the Medical Research Council Committee on Influenza and other Respiratory Virus Vaccines

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GEOMETRIC MEAN TITRES AND RISES OF HÆMAGGLUTINATING ANTIBODY

	No of doses of vaccine	Geometric means (reciprocal of titre)								Rises			
		Initial titre ≤ 1/5 *				Initial titre > 1/5				Initial titre ≤ 1/5*		Initial titre > 1/5	
		No of volunteers	1st sample	2nd sample	3rd sample	No of volunteers	1st sample	2nd sample	3rd sample	1st to 2nd	1st to 3rd	1st to 2nd	1st to 3rd
History of influenza-like illness	1	7	≤ 5	38	37	9	39	216	127	> 7·6	7·4	5·5	3·3
	2	5	≤ 5	38	89	12	35	191	232	> 7·6	18·0	5·5	6·6
No history of influenza-like illness	1	20	≤ 5	16	21	5	18	111	86	> 3·2	4·2	6·2	4·8
	2	18	≤ 5	28	122	7	35	202	214	> 5·6	24·4	5·8	6·1
All volunteers	1	27	≤ 5	20	21	14	29	170	110	> 4·0	4·2	5·9	3·8
	2	23	≤ 5	30	113	19	35	196	225	> 6·0	22·6	5·6	6·4

* Where result was quoted as being < 1/10, it was assumed to be ≤ 1/5

The vaccine was prepared from A/Singapore/1/57, containing about 7000 hæmagglutinating units per dose of 1 ml, by Dr F Himmelweit of the Wright-Fleming Institute

Material and Methods

Two Royal Air Force stations with different attack-rates during the epidemic were chosen for the trial Station A, which had a mild outbreak causing an admission-rate to sick quarters of 12%, provided 26 volunteers who had had no clinical respiratory illness during the epidemic Station B had a severe outbreak of influenza A (Asian) with an admission-rate to sick quarters of 40% 57 airmen from this station volunteered 33 of these had had a clinical illness resembling influenza during the epidemic, the rest had not been ill

All these volunteers received one dose of vaccine Half of each group, picked by use of a table of random numbers, received a second similar dose three weeks later Members of each group were bled (into evacuated 'Venules') before the first inoculation, and again at intervals of three and six weeks The serum was separated and stored at –20°C When all samples had been collected they were divided at random between the laboratories of Mill Hill and Sheffield, where the serological tests were made Those testing the sera did not know from which group the samples had been obtained. Antihæmagglutination tests were performed with the A/Singapore/1/57 virus and the sera treated with *Vibrio choleræ* extract, according to the recommendations of the W H O expert committee (World Health Organisation 1953)

There was no respiratory illness among the volunteers during the period of the trial It was found that of those with no clinical history of influenza during this epidemic only 24% had antibodies before inoculation, whereas 64% of those with a clinical history of influenza had antibodies before inoculation

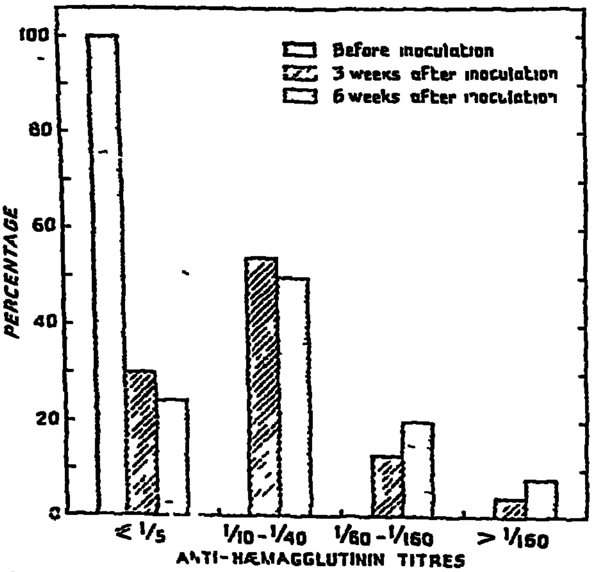

Fig 1—Distribution of titres 3 and 6 weeks after a single inoculation of vaccine in 27 individuals with initial antibody titres of ≤ 1/5

Results

The antihæmagglutination titres in the vaccinated individuals are summarised in the table and figs 1–4 The titres are shown in the figure as the percentages of individuals with titres within a given range, and figs 1–4 show antibody distributions in individuals with initial antibody titres of 1 in 5 or lower and in those with initial titres higher than 1 in 5, inoculated with one or with two doses of vaccine

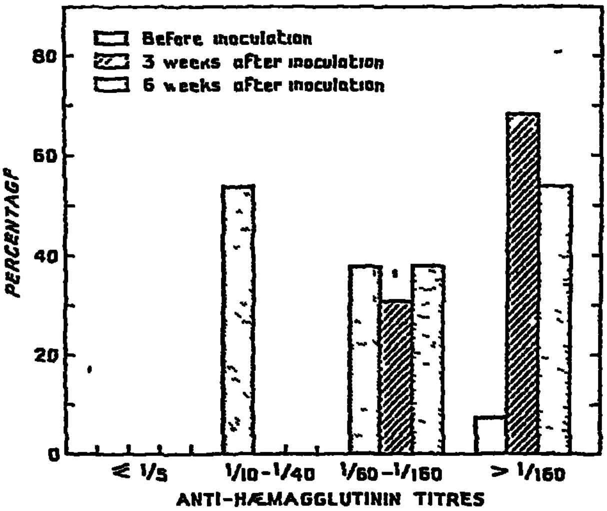

Fig 2—Distribution of titres 3 and 6 weeks after a single inoculation of vaccine in 14 individuals with an initial antibody titre of > 1/5

The table and fig 1 show that people with no initial antihæmagglutinin reacted poorly to a single dose of Asian vaccine. This finding agrees with the results of many other workers—e g, Commission on Influenza (1957), Medical Research Council Committee on Influenza and other Respiratory Virus Vaccines (1958)

On the other hand, a single inoculation of the same vaccine gave a much better response in individuals with initial titres of 1 in 5 or more (fig 2) due to virus-A infection—in most cases associated with a clinical attack of influenza in the epidemic This is also illustrated in the table, showing a higher geometric mean titre after inoculation This suggests that previous experience with this antigen had sensitised the antibody-producing mechanism, and in support of this the results in fig 3 and the table indicate that two inoculations of vaccine, given at an interval of three weeks to individuals without initial antibody, led to a good *secondary* response Comparison of figs 1 and 3 shows that the high titres after two inocula-

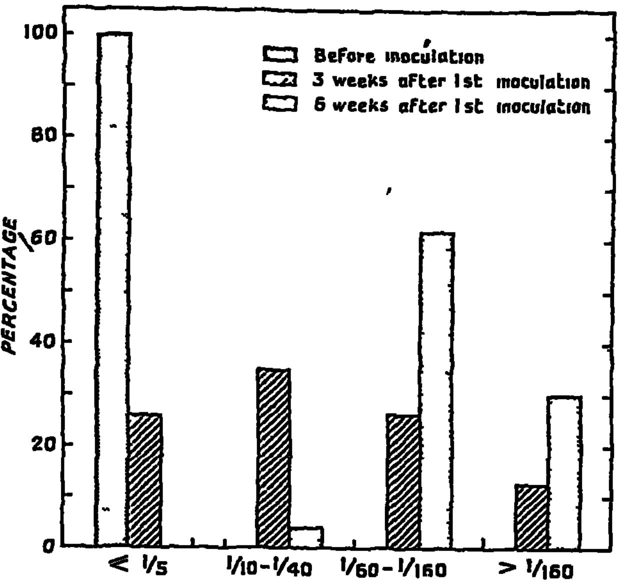

Fig 3—Distribution of titres 3 and 6 weeks after initial inoculation in 23 individuals with an initial antibody titre of < 1/5, given two doses of vaccine at 3-week intervals

tions cannot be due to a delayed response to the first inoculation

From fig 4 and the table it is clear that individuals with initial antibody titres of 1 in 5 or more received a booster effect from a single dose of vaccine but did not develop much higher titres from a second dose of vaccine Beveridge (1944) found that individuals vaccinated with REL and LEE strains of influenza virus A and B did not get a better response from two doses of vaccine given at an interval of two weeks than from a single dose The present results confirm his conclusion for viruses of which the inoculated individuals have had previous antigenic experience But with new influenzal antigens it appears that two antigenic stimuli are needed to produce a good antibody response

These results indicate the requirements for a good serological response, but they tell us nothing of the requirements for protection Unfortunately the clinical trials designed to compare one dose with two doses of Asian vaccine could not be carried out because the epidemic came too early

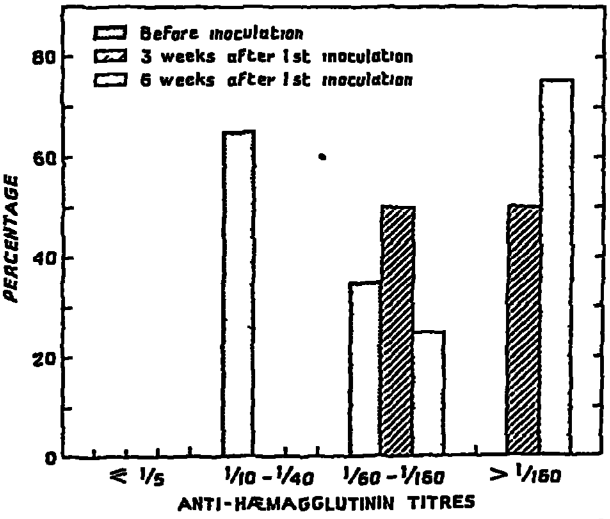

Fig 4—Distribution of titres 3 and 6 weeks after initial inoculation in 19 individuals with initial antibody titres of > 1/5, given two doses of vaccine at 3-week intervals

This, and most other serological trials, measured only hæmagglutination-inhibition antibody, and it is not known what relation this may have to protective antibody, nor indeed whether protection is due to circulating antibody or to the sensitisation of the protective mechanism—of which the antibody response may only be an indication Evidence that one injection of Asian-influenza vaccine may provide sufficient protection is given by the result of the M.R C trial, which gave a protection-rate of 52-67% immediately after vaccination, this compares well with previous trials in individuals who had previously experienced related influenza-A antigens (Commission on Influenza 1944)

Summary

A serological trial of an Asian-influenza vaccine was carried out in 83 volunteers, all of whom had been exposed to the autumn influenza epidemic 33 had had a clinical illness resembling influenza Volunteers with no initial antihæmagglutinin reacted poorly to a single dose of vaccine A much better serological response was obtained with a single dose in individuals with initial titres of 1 in 5 or more Two inoculations given to individuals without initial antibody led to a good secondary response This is contrary to previous experience, and it is suggested that two antigenic stimuli are needed to produce a good antibody response in people who have not previously experienced this antigen, whereas one is probably sufficient for those that have

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DIABETIC RETINOPATHY AND NEPHROPATHY IN PANCREATIC DIABETES

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The ætiological relationship of the vascular complications of diabetes mellitus to the disorder itself is the subject of much interest and controversy In a panel discussion on this problem, LeCompte (1957) has recently said that there is little evidence against the view that they may be determined by the same gene, since there are very few reported cases of capillary lesions in diabetes due to some known cause, such as pancreatitis or pancreatic fibrosis

We report here the development of a specific diabetic retinopathy and the occurrence of glomerulosclerosis of the type specific to diabetes mellitus, in a patient whose diabetes is believed to have been due to chronic pancreatitis, and we discuss the implications of these findings

Case-report

A man, aged 48, an architect, was said to have had "nephritis" following mumps in 1920, at the age of 11, and for a few years after this had experienced episodes of vague abdominal discomfort In 1928, when he was 19, he developed the classical symptoms of diabetes mellitus, was found to have considerable glycosuria, and was treated by dietary restriction and the administration of insulin Except when he had a severe infection, the daily dose of insulin varied from 28 to 40 units

In 1936 he noticed that his stools were pale and floated in water, and that he had lost weight In 1947 he complained of episodes of nocturnal diarrhœa, with the incontinent passage of pale fluid fæces In 1952 he had developed neuropathy in his legs, with absence of ankle reflexes, diminution of knee reflexes, some wasting of the calf and adductor muscles, loss of appreciation of vibration and pain, and absence of sweating in the lower limbs At this time diabetic retinopathy was first detected, a few microaneurysms and one or two round specks of hyalinisation were visible in both retinæ. In the next two years two classically painless indolent ulcers developed on his feet, he became impotent and was found to have a large distended bladder, unassociated with discomfort, which could not be voluntarily evacuated The dynamics and chemistry of the cerebrospinal fluid (C.S F) were normal and the Wassermann and Kahn reactions of serum and C.S F negative Many courses of various antibiotics were given for urinary tract infections A little protein was discovered in the urine for the first time in association with the infection In 1957, incontinence and recurrent infection became so severe that both ureters were transplanted to an isolated loop of ileum which acted as a reservoir, but in spite of this the patient died within a few months of urinary tract infection, toxæmia, and uræmia At the time of death he had moderately severe diabetic retinopathy (fig 1) During the last two years of his life his blood-pressure was about 150/105 mm. Hg, there was never any evidence of congestive heart-failure

During the thirty years of his diabetic life, hypoglycæmic episodes were exceptionally frequent, occurring up to three or four times a week, irrespective of the preparation of insulin used, and frequently required his admission to hospital During one of these admissions, in 1955, the clinical diagnosis of steatorrhœa was confirmed by fat-balance studies which showed an absorption of 60% of ingested fat, the stool contained, on average, 50 g of fat and 6 6 g of nitrogen per day Radiography of the abdomen showed extensive calcification of the pancreas (fig 2) and the results of analysis of the duodenal aspirate following the injection of secretin and pancreozymin confirmed the complete absence of exocrine pancreatic function, there being virtually no response in the pH, rate of flow, or bicarbonate, amylase, trypsin, or lipase content Subsequent treatment with pancreatin materially improved the steatorrhœa but not the nocturnal diarrhœa

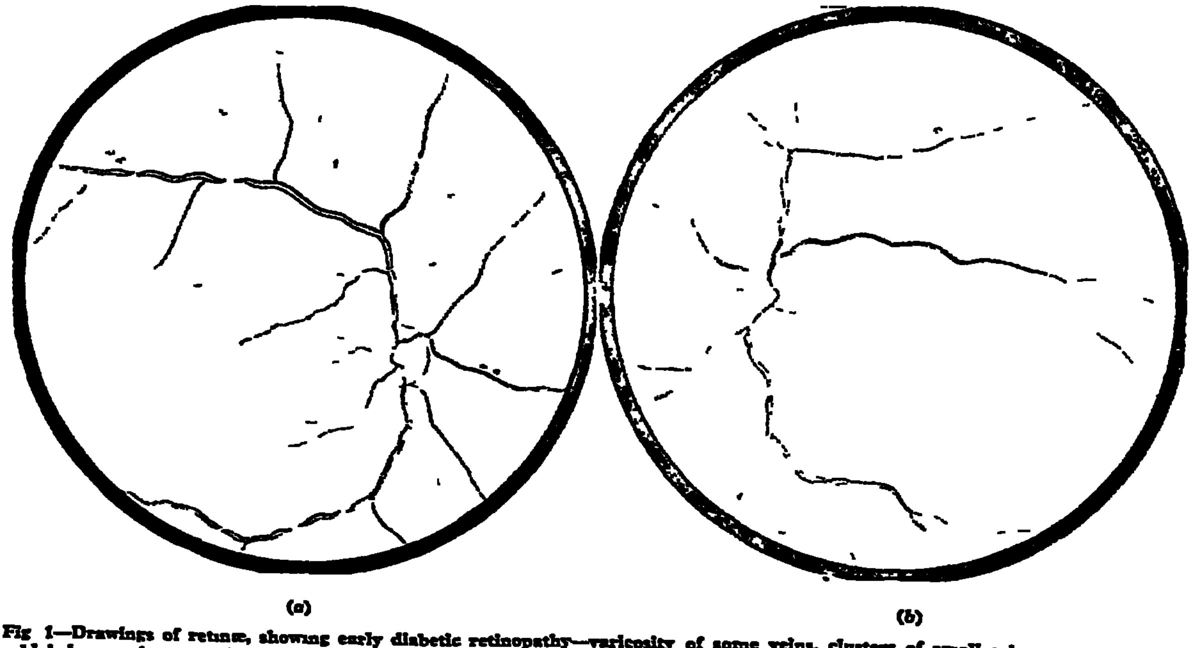
Fig 2—Oblique film of abdomen, showing calcification of pancreas

There was no family history of diabetes His parents died in their 70s, none of their parents or siblings had diabetes He had two elder brothers alive and well, and both they and the patient were of normal weight at birth

Necropsy Findings

The necropsy was carried out two hours after death

Pancreas—32 2 g (fig 3) The organ consisted mainly of fibrous tissue and nodules of calcium, very little true pancreatic tissue could be identified. The main pancreatic duct could not be found from the duodenal aspect, but in the head of the pancreas it could be seen distended by a small white calculus, 0 3 cm in diameter



(a) (b)

Fig 1—Drawings of retinæ, showing early diabetic retinopathy—varicosity of some veins, clusters of small micro-aneurysms, round blob hæmorrhages, and discrete exudates (a) right eye (b) left eye.

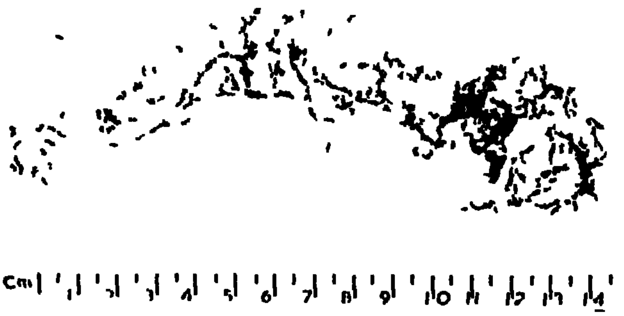


Fig 3—Pancreas, showing gross calcification

Kidneys —Right 300 g, left 225 g Both organs showed moderate hydronephrosis with chronic pyelonephritic scarring, and there were small soft calculi in the left pelvis and calyces A large perinephric abscess was found in continuity with a small abscess in the upper pole of the right kidney The perinephric abscess had tracked down the right psoas muscle into the right inguinal region and behind the pubes into the left groin

Heart —310 g There was slight left ventricular hypertrophy

Coronary arteries and aorta —These vessels contained only occasional tiny plaques of atheroma

Lungs —There was patchy collapse of the right lower lobe

Liver and bile-ducts —2080 g The organ was enlarged and congested The biliary tract was patent

Adrenal glands —Combined weight 16 7 g They were both slightly enlarged

Pituitary —0 55 g The gland was a little smaller than usual

No significant abnormalities were found in the other organs

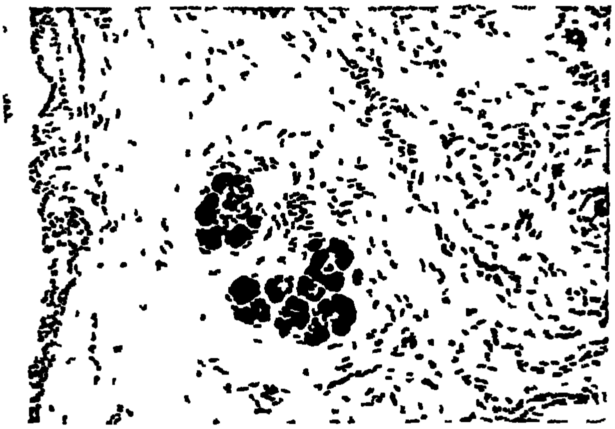


Fig 4—Pancreas, showing gross fibrosis and remaining foci of acinar tissue Squamous metaplasia is seen in a greatly dilated duct (Hæmatoxylin and eosin ×100)

Histology

Pancreas —Representative sections were taken from head, body, and tail, and stained by the hæmatoxylin and eosin method and with Gomori's chrome alum hæmatoxylin phloxine for α and β islet cells (Gomori 1941) Only occasional small islands of exocrine tissue had survived and were situated in dense fibrous tissue (fig 4) Most of the ducts and ductules were dilated and many were filled with inspissated secretion and cell debris showing varying degrees of calcification Squamous metaplasia of the duct epithelium was a feature in many areas Islet tissue was also greatly reduced in amount Small localised groups of islets were found in the fibrous tissue, and in none was there evidence of fibrosis, hyalinisation, or any other lesion associated with diabetes mellitus (fig 5)

Good differentiation of α and β cells with Gomori's stain was technically difficult because of the nature of the tissue, but as far as could be ascertained the α/β cell ratio was not abnormal

Kidneys —There was fairly extensive pyelonephritic scarring in both kidneys Many of the glomeruli exhibited diffuse intercapillary sclerosis (fig 6) and a few contained small but typical nodular lesions of classical diabetic glomerulosclerosis (fig 7) The latter varied from 20µ to 50µ in diameter There was moderately severe hyaline arteriolosclerosis

Testes —Both showed severe atrophy of the seminiferous tubules No spermatogenesis could be seen, and the tubules, whose basement membranes were considerably thickened, were lined mainly by Sertoli cells The interstitial cells were increased in number There were groups of histiocytes containing hæmosiderin in the interstitial tissue but no fibrosis or chronic inflammatory changes were seen

Heart —Early brown atrophy was present

Liver and spleen —These organs were congested

Lungs —There was purulent bronchitis, and collapse in the right lower lobe

Parotid glands —There were a few foci of fibrosis and lymphocyte infiltration, associated with glandular atrophy, but the glands otherwise appeared normal.

Adrenal and pituitary glands —No histological abnormality

Nervous system —Complete demyelination and fibrous replacement was found in peripheral nerves from the left leg and in the "presacral nerve" There was partial demyelination and fibrosis of posterior nerve-roots No abnormality of the spinal cord or brain could be seen

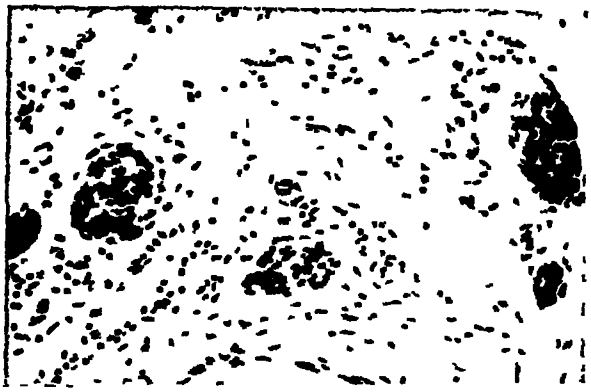


Fig 5—Pancreas showing a few islets in dense fibrous tissue (Hæmatoxylin and eosin ×175)

Discussion

The successful therapeutic use of insulin has so reduced the incidence of diabetic coma that very few diabetic patients now die from this cause (Duncan 1951) However, although the life-expectancy of the average patient with diabetes is only a few years shorter than that of the general population (Metropolitan Life Insurance Company 1947), the majority sooner or later develop one or more of the so-called degenerative changes (Mirsky 1946, Dolger 1947, Lundbaek 1954) In contrast to the neuropathic changes, the vascular lesions in the eye and kidney are generally considered to be specific to the disorder (Becker 1952, Leiter 1955, Lukens 1955) So frequently

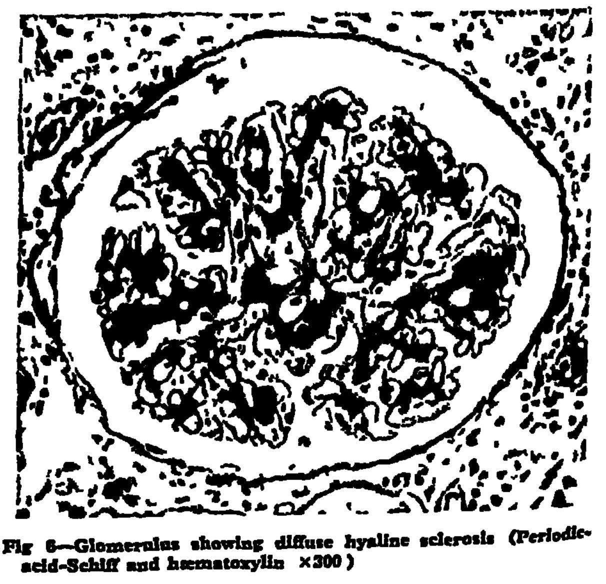


Fig 6—Glomerulus showing diffuse hyaline sclerosis (Periodic-acid-Schiff and hæmatoxylin ×300)

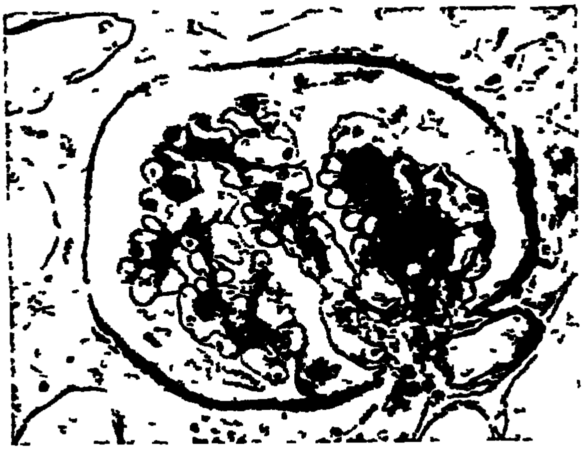


Fig 7—Glomerulus showing nodular lesion of classical diabetic glomerulosclerosis (Periodic-acid-Schiff and hæmatoxylin ×300)

do these changes accompany longstanding and poorly controlled diabetes that some authorities look upon them as an integral part of the disease rather than as complications of it (Dolger 1947, Henderson et al 1947)

There is little doubt that the predisposition to diabetes mellitus is often inherited, being most probably transmitted as a recessive characteristic, though it manifests itself clinically in only a proportion of those bearing the gene (Steinberg 1955) The tendency to develop the specific vascular changes could similarly be inherited, but the fact that they have not been found with certainty in persons having no demonstrable defect of carbohydrate metabolism (Becker 1952, Mirsky 1952) makes it improbable that they are inherited as an independent diathesis For the same reason, even if they were transmitted in close association with the diathesis of idiopathic diabetes (Dry and Hines 1941, White and Waskow 1948, LeCompte 1957), their development must depend on the presence of the metabolic disturbance of diabetes, of which the abnormality in carbohydrate metabolism may be only a part

Reproduction of the lesions of the specific retinopathy or nephropathy in animals made hyperglycæmic by one or other of a variety of techniques would demonstrate that a hereditary basis is not necessarily involved Such attempts have not been unequivocally successful (Lukens and Dohan 1946, Foglia et al 1948, Friedenwald 1950, 1952, Mann et al 1951, Becker 1952, Rickets 1952, Janes and Bounds 1954, LeCompte 1957) Nevertheless, these were short-term experiments, and it may be that the duration, as well as the degree of control, of the diabetes favours the development of these retinal and glomerular changes in man

Hyperglycæmia, impaired glucose tolerance, and the tendency to develop ketosis can arise in man as the result of disease of the pancreas The development of the specific retinopathy or nephropathy in such "pancreatic diabetics" would support the view that these complications result from the abnormal metabolism in diabetes rather than as a consequence of an inherited defect So far as we know, only two such cases have been previously reported

Sprague (1947) described a patient who developed relapsing pancreatitis at the age of 27 and became diabetic eight years later After a further nine years he was found to have a specific diabetic retinopathy

The presence of diabetic retinopathy was recorded by Hudson (1953) in a man, aged 50, suffering from hæmochromatosis who had developed diabetes fifteen years previously

Three other cases are described in personal communications

Stawell, in a personal communication to Lawrence (1949), mentions diabetic retinopathy in a patient with diabetes due to hæmochromatosis, Rynearson (1957) describes a patient who developed diabetic retinopathy three years after the onset of diabetes which followed total pancreatectomy, and Dunlop (1957) records the presence of the specific retinopathy in a patient with longstanding diabetes resulting from hæmochromatosis

The details of Stawell's patient are not known, but in none of the other patients was there a family history of diabetes, and the diabetes was regarded as purely pancreatic in origin

We believe that the diabetes in our patient was also a true "pancreatic diabetes," there being several clinical features which suggested that his diabetes was due to insulin lack alone rather than to the operation of any anti-insulin mechanisms

(1) The sensitivity to the blood-glucose-lowering action of insulin (his blood-glucose was noted on several occasions to fall from over 600 mg to less than 50 mg per 100 ml four to six hours after the subcutaneous injection of 12 to 20 units of soluble insulin), this probably accounted for the extraordinary frequency of the hypoglycæmic episodes, even with a moderate daily dose which varied from 28 to 40 units, except when infection necessitated the administration of larger doses This tendency to hypoglycæmia remained unaltered throughout the entire course of his disorder

(2) His failure to show any reduction in the concentration of glucose in the blood in response to a dose of 4 5 g of carbutamide by mouth the immediate hypoglycæmic effect of carbutamide is believed to be due to the release of insulin from the β-cells of the pancreas, and its absence in this patient suggests that the pancreas was unable to secrete insulin (Houssay and Phenos 1956, Fajans et al 1956)

(3) The clinical and biochemical evidence of extensive disease of his pancreas was overwhelming With duodenal intubation no exocrine secretion could be demonstrated in response to stimulation by secretin and pancreozymin, and the stool nitrogen content was elevated The steatorrhœa thus appears to have been of pancreatic origin From the patient's observation, pale stools were present eight years after the onset of the diabetes, and this suggests that disease of the pancreas was present at that time The ætiology of the pancreatic lesion is, however, obscure Mumps contracted at the age of 11 may have some causal relationship, and the history of vague episodes of abdominal discomfort during adolescence suggests that pancreatitis had already developed Diabetes may precede the steatorrhœa, and not uncommonly develops within a few years of the first attack of pancreatitis (Maimon et al 1948)

(4) Finally, the fact that, as far as can be ascertained, none of his known relatives has or had diabetes, is consistent with the view that he had not inherited a diabetic diathesis

The clinical diagnosis of severe pancreatic insufficiency was confirmed by the finding of gross pancreatic fibrosis at necropsy The reduction in the amount of islet tissue from the normal appears quite sufficient to account for the patient's diabetic state on the basis of insulin deficiency The hypothesis that he might have had a coincidental diabetic diathesis is not supported by the histological appearance of the few remaining islets No hyalinisation or other lesion associated with idiopathic diabetes mellitus could be found, and the proportion of α to β cells seemed to be within normal limits (MacLean and Ogilvie 1955) The appearance of the pancreas was consistent with pancreatitis due to mumps The presence of the calculus in the main pancreatic duct is probably not of ætiological significance, since marked calcification was scattered throughout the pancreatic tissue and in most of the ducts

It was unfortunately not possible to examine histologically the retinopathy visible on clinical examination, but the latter is sufficient to establish its specificity The presence in the kidneys of typical Kimmelstiel-Wilson bodies was established by the histological examination, though they were few - The diffuse glomerulosclerosis was also thought to be diabetic in nature and to conform to the descriptions by Bell (1953) and Lambie and MacFarlane (1955) It is, however, not as specific to diabetes mellitus as the nodular lesion, since similar changes may be found in type-II glomerulonephritis

The problem of the relationship between diabetes and the later development of its specific complications will probably remain unsolved until a more intimate knowledge of the biochemical abnormality in diabetes and in the tissues affected by the degenerative changes is available Nevertheless, the development of these changes in patients whose diabetes appears to be of pancreatic origin is very strong evidence in favour of the view that they are to a large extent the consequence of the metabolic disorder which results from insulin deficiency Reports of patients similar to our own would be of great value in throwing further light on this problem, which is not merely an academic one The emphasis commonly placed upon the need for rigid diabetic control will be fully justifiable only if it can be shown that the development of these complications is dependent on or influenced by a derangement of metabolism, and that they are not an inescapable consequence of inheritance

Summary

The precise relationship between the development of the specific vascular complications of diabetes mellitus in the retinæ and of specific nodular glomerulosclerosis to the disorder itself is unknown A patient has been described in whom both these complications occurred and in whom there was overwhelming evidence to support the view that the diabetes arose as a result of pancreatic disease The significance of this case in relation to present-day views of the ætiology of these complications is discussed It constitutes strong evidence in favour of the view that these complications are the consequence of the metabolic disorder which results from insulin deficiency

For permission to report this case we are grateful to Prof D M Dunlop and Sir Stanley Davidson, in whose charges the patient was investigated We thank Prof G I Scott and Miss C Gundry for the ophthalmoscopic examination and drawings, Dr I N Marks who carried out the tests of the pancreatic function, and Mr T C Dodds, of the department of medical photography, for the photographs

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TWENTY-NINE CHILDREN WITH SULPHONAMIDE HÆMATURIA

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Shortly after the introduction of sulphonamide therapy, hæmaturia was noted as an occasional complication

The explanation seemed to be that, as urine passes along the renal tubules, it becomes more concentrated and acid, with the result that crystals of sulphonamide may be deposited The convoluted tubules are first affected (Goodman and Gilman 1955), but deposition of crystals can spread in either direction and give rise to hæmaturia, albuminuria, oliguria, hypertension, or nitrogen retention Such cases may present with anuria (Atkinson 1957, Browne 1957) or more rarely with obstruction of the urethra (Miller and Mitchell 1952, Rice-Edwards 1950) These happenings may be attributable to overdosage of sulphonamide, inadequate intake of fluid, or the use of a preparation unduly liable to crystallise out at pH values found in the renal tubules

In the ten years since 1948, a total of 29 patients have been treated in the medical wards of The Royal Hospital for Sick Children, Glasgow, for hæmaturia associated with taking sulphonamide drugs In all of them

1 The patient had had sulphonamide therapy before the symptoms began
2 There were no history or subsequent findings suggestive of renal disease (except those occasioned by sulphonamide crystallisation)
3 Gross hæmaturia and crystalluria were present

The presence of urinary sulphonamide was confirmed in almost all cases and the serum sulphonamide level estimated in some

Clinical Observations

The ages of the 29 children ranged from 1 to 12 years, most being between 1 and 6 Sulphonamide had been given for periods of one to six days in daily doses of 100–400 mg per kg body-weight The blood-pressure was elevated in 14 of the 22 cases in which it was recorded, but it returned to normal levels within a few days The non-protein-nitrogen content of the blood was raised on 13 of the 21 occasions in which the estimation was made The hæmaturia lasted one to six days, and albuminuria usually persisted a few days longer

In 3 cases anuria persisted for more than forty-eight hours, uræmia was present in all three

Case 1 —A girl, aged $6^1/_2$, was given sulphamerazine 2 g daily for two days because of upper respiratory infection She then complained of loin pain, and developed hæmaturia followed by anuria After forty-eight hours' anuria her blood-pressure rose to 148/110 mm Hg, and she had severe convulsions—probably due to hypertensive encephalopathy The blood non-protein nitrogen was 125 mg per 100 ml

Lumbar puncture, venesection, sedation with phenobarbitone, and hypertonic solutions intravenously were employed before her convulsions ceased She was given sodium bicarbonate gr 180 daily, and diuresis began shortly after this was started Within fourteen days she was symptom-free

Case 2.—A boy, aged 2, was given four doses of sulphamerazine, each 0 5 g orally, as treatment for a sore throat. He vomited, and developed hæmaturia and anuria Anuria persisted for seventy-two hours, during which time the blood non-protein-nitrogen rose to 140 mg per 100 ml and the blood-pressure to 114/80, and he became fevered Sodium bicarbonate gr 180 daily was given and fluid intake restricted to 1 litre daily Diuresis began and he became symptom-free ten days later

Case 3—A girl, aged 2, was given 2 5 g of sulphamerazine daily for four days for a respiratory infection She then passed "grains of sand" per urethram, and stopped passing urine Sixty hours later she was admitted to hospital; the urethra was cleared and she voided urine Treatment was begun with sodium bicarbonate gr 180 daily She had anuria for a further forty-eight hours, during which time she was restless and anorexic, and her blood-urea rose to 147 mg per 100 ml Her blood-pressure was 150/70, her serum-sodium level had fallen to 114 mEq per litre and serum-potassium to 3 8 mEq Supplementary potassium was added to her intake of 250 ml of 25% glucose solution daily, and diuresis began after five days of anuria This urine contained erythrocytes and sulphonamide and her serum-sulphamerazine content was 13 8 mg per 100 ml, more than a hundred hours after oral therapy had stopped

As the following table shows, 27 of these 29 children had been given a preparation containing sulphamerazine

Drug	No of cases	Dosage mg per kg per day
Sulphamerazine	26	100–400
Sulphasomidine	1	200
Sulphadimidine	1	?
Triple sulphonamide *	1	210

* A mixture of sulphamerazine, sulphathiazole, and sulphadiazine.

One specific brand of aqueous suspension was prescribed for 22 of these 27 cases In 13 the dose of sulphamerazine had been 100–200 mg per kg per day, in 7 it had been 200–400 mg per kg per day, and in the remainder indeterminate

Our treatment in these cases was essentially conservative Administration of sulphonamide was stopped, and, where excretion of urine was adequate, copious fluids were given together with sodium bicarbonate gr 30 four-hourly When anuria and uræmia arose, fluid intake was restricted and glucose administered Hypertensive encephalopathy was treated by sedation, lumbar puncture, and venesection

This cautious approach to treatment seems justified in that all cases to date have recovered completely

Discussion

The dosage of 'Cremomerazine' recommended by the manufacturers for the first four years of life amounts to about 110–220 mg per kg for the first day and about 70–140 mg per kg per day thereafter (dosage refers to sulphamerazine content) It is disturbing to find that 13 of the present patients were receiving doses which approximated to such levels of dosage, though in most cases the drug had been given more frequently than twelve-hourly 1 boy had received only 2 g (190 mg per kg) when anuria began There is no evidence that the fluid intake of these children was restricted It may be true that, under ideal conditions, with twelve-hourly doses and copious fluid and alkali administration, sulphamerazine seldom produces hæmaturia, but the overriding consideration here is that in actual practice this drug may cause hæmaturia, azotæmia, and hypertension in children when given at a dosage level in frequent use To justify giving a drug potentially noxious in therapeutic doses one must show that it has significant advantages over other preparations Sulphamerazine seems to me to have no outstanding virtue which would lead me ever to prescribe it.

Many cases of sulphamerazine hæmaturia have been reported (Sheppard 1948, Atkinson 1951, Brand 1951, Rendle-Short 1951, Morton and Dobbs 1951), but probably many more cases with slight hæmaturia have not been recognised There is a risk that hæmaturia following the treatment of upper respiratory infections with sulphamerazine might simulate acute hæmorrhagic nephritis and so mislead the clinician -

Summary

29 cases of hæmaturia following administration of sulphonamide drugs are recorded Anuria, hypertension, encephalopathy, and uræmia were seen in some patients, but all subsequently recovered

27 of these patients had been given sulphamerazine, and in many cases the dose was not excessive as judged by one manufacturer's recommendations It seems doubtful whether the use of this drug is justified.

I should like to thank Prof Stanley G Graham and Dr J H. Hutchison for allowing me to use their case-records

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METHOD OF ESTIMATING THE DIAMETER OF ERYTHROCYTES

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THE diameter of the erythrocytes can be measured by many methods, most of which are rather laborious and require special equipment. A fairly simple method, requiring no special equipment, is to spread a blood film from a normal control on top of a stained film with the erythrocytes to be measured, and then to compare the relative sizes of stained and unstained erythrocytes This method has for many years been occasionally used in Norway, and undoubtedly in many other countries Bessis (1956) mentions the method, giving Pittaluga the credit for introducing the method to him

This method of superimposed blood films has, however, certain drawbacks it is difficult to make both films thin enough in the same places to avoid overlapping of stained and unstained erythrocytes, the stained film is often scratched when the superimposed unstained film is being spread, and the process of staining might change the

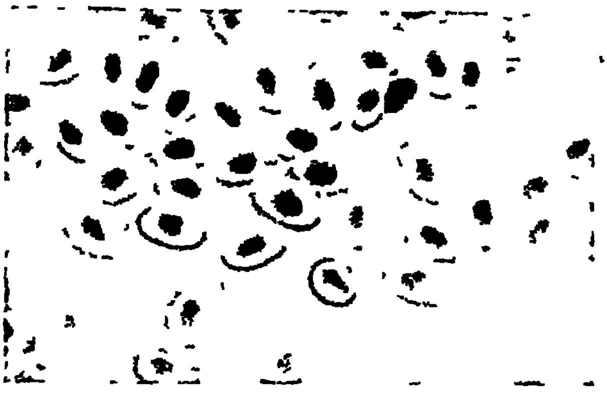

Fig 1—Hens' erythrocytes

size of the erythrocytes—but this change in size is usually surprisingly small.

All these difficulties would be avoided if one could mix blood from the unknown and the control before spreading the film and still be able to decide which erythrocytes in the film belonged to the unknown and which to the normal control. Erythrocytes of birds are elliptical and contain a nucleus—features which clearly distinguish them from human erythrocytes. We have lately made films from a mixture of hens' blood and human blood and have estimated the size of the human erythrocytes by comparing them with the hens' erythrocytes.

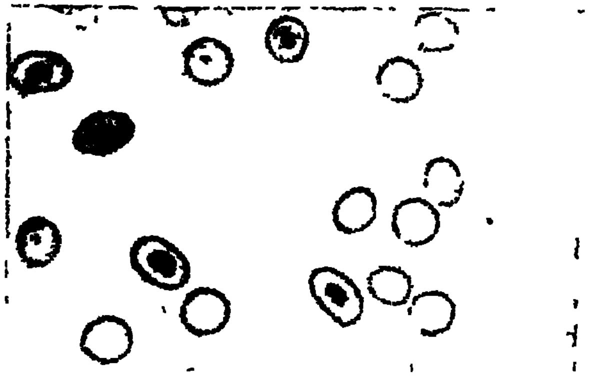

Fig 2—Mixture of normal human and hens' erythrocytes

Heparinised blood is collected from a killed hen and may be kept in the refrigerator for days or weeks until needed. Two drops of hens' blood is added to 0·5 ml. of heparinised or oxalated human blood, and a film is made from the mixture and stained with Wright or Giemsa stain. Hens' erythrocytes are elliptical, with a longitudinal diameter of about 11·0 μ and a lateral diameter of 6·7 μ (90% of hens' erythrocytes have a longitudinal diameter between 9·8μ and 12·2μ, and 90% have a lateral diameter between 5·8μ and 7·6μ). The size of a particular hen's erythrocytes is checked against a normal human control before the hen's blood is used for estimating the size of human erythrocytes.

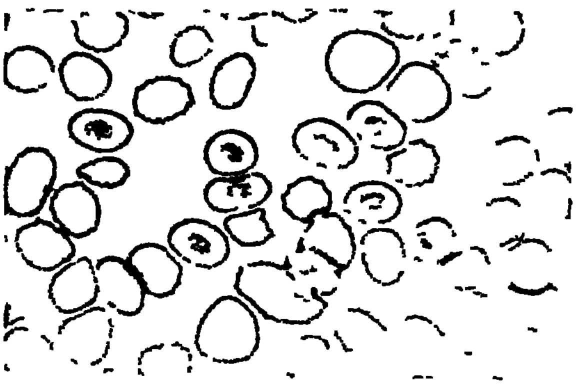

Fig 3—Mixture of human erythrocytes from a patient with pernicious anæmia and of hens' erythrocytes

If one does not want to keep a supply of hens' blood in the refrigerator, two drops of blood is easily obtained from a cut in a hen's comb.

Fig. 1 shows a stained film of hens' blood, fig. 2 a film made from a mixture of hens' blood and normal human blood, and fig. 3 a film from a mixture of hens' blood and blood from a patient with untreated pernicious anæmia.

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ONE RADIOGRAPH TO EXCLUDE PLACENTA PRÆVIA

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Placenta prævia may present as either antepartum hæmorrhage or (without antepartum hæmorrhage) as malpresentation, unstable position, or a high fœtal head. The modern management of placenta prævia has drastically reduced maternal and fœtal mortality (see table).

Expectant treatment (Macafee 1945, 1946, Johnson 1945, 1950, Grant 1955) aims to continue the pregnancy into the 37th week, when the fœtus has every chance of surviving. The patient has to be admitted for 1–6 weeks before a low implantation of the placenta can be excluded or confirmed. Under anæsthesia the lower uterine segment is examined digitally through the cervix. If the placenta is then detected anterior to but not beyond the internal os of the uterus, the membranes are ruptured, but if it is palpable in any other position, immediate lower-segment cæsarean section is the treatment of choice. If the placenta is not palpable, the pregnancy may be allowed to terminate spontaneously.

Our object was to find a reliable simple diagnostic method, so that those patients who were conclusively found not to have a placenta prævia could be spared a long stay in hospital. We wished to avoid both unnecessary filling of valuable hospital beds and the emotional strain experienced by many mothers because of enforced absence from their homes and families, as well as the taking of numerous radiographs for localising the placenta; this may be dangerous because of irradiation of the fœtus (Stewart et al. 1956) and the mother (Medical Research Council 1956), and is expensive in film and the time of highly skilled staff.

We have investigated the accuracy and practical value of a single lateral radiograph of the uterus in cases of suspected placenta prævia.

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Material and Methods

107 patients were investigated between January, 1953, and June, 1956 The position of the placenta was estimated radiographically *only* if the information would help in the clinical diagnosis Antepartum hæmorrhage, malpresentation, unstable lie, or high fœtal head were the indications for radiography

The apparatus consisted of a standard four-valve X-ray unit with a rotating anode tube and tilting table

Three radiographs were taken routinely in each patient These were lateral views of the uterus, the pelvis in the erect position, and the pelvis in the semi-erect position

The films were read on a standard viewing-box Separate illumination by a 100-watt bulb was necessary for viewing the anterior aspect of the uterus and adjacent abdominal wall. A wedge filter was not used while taking the radiographs

Various radiographic techniques have been developed to find the position of the placenta Soft-tissue radiography (direct placentography) has proved the most valuable (Snow and Powell 1934, Dippel and Brown 1940, Bishop 1945, Reid 1949, 1951, 1953, Stallworthy 1950, 1951, Murray 1953, Hartley 1954, Dawson and Mitchell 1954) Further information is obtained by radiographic measurement of the displacement of the fœtal head from the sacral promontory and symphysis pubis at the pelvic brim (indirect placentography) (Ball and Golden 1941, McCort et al 1944, Bishop 1945, Reid 1951)

Cystography (Ude et al 1934, Dippel and Brown 1940) is not generally used now because it is unreliable

Amniography (Menees et al 1930, Kerr and McKay 1939, Savignac 1953, Williams 1956), aortography (Hartnett 1948), retrograde femoral arteriography (Sutton 1952), and localisation of the placenta by radioactive sodium (Browne 1951) are experimental techniques

Both direct and indirect placentography were used during this investigation As a precaution, the patient was asked to empty her bladder and rectum before being radiographed

Results

The placenta was correctly identified in the upper uterine segment in 90 of the 107 cases At the beginning of the investigation the placenta in 1 of the 107 cases was wrongly interpreted as entirely in the upper segment, examination under anæsthesia revealed a second-degree anterior placenta prævia

Using soft-tissue and displacement radiographic techniques, placenta prævia was missed in 3 cases, and correctly diagnosed in 12 cases, the radiographic findings were inconclusive in 2 cases It was observed that, if there was no placental shadow in the upper uterine segment, placenta prævia was likely to be found clinically In practice, these patients must be admitted, most have placenta prævia

Of the 90 cases in which the placenta was correctly identified in the upper uterine segment, 54 were associated with antepartum hæmorrhage The causes of antepartum hæmorrhage were analysed as follows

No cause found	30	Erosion of cervix *	3
Abruptio placentæ	16	Varicosities of cervix	1
Circumvallate placentæ	3	Polyp of cervix	1

* 1 case proved to be invasive carcinoma of the cervix

Discussion

The most significant conclusion reached was that radiological evidence of the placenta in the upper uterine segment is highly accurate, a lateral radiograph of the uterus taken after 34 weeks' gestation, in the absence of hydramnios, yielded the necessary information to exclude placenta prævia It was found that the management of 90 out of the 107 patients investigated could have been decided with accuracy on the evidence of single lateral radiograph of the uterus

MORTALITY-RATES IN PLACENTA PRÆVIA

Treatment	Series	Maternal mortality (%)	Fœtal mortality (%)
Active (pre-modern)	Berkeley (1936) Browne (1939)	7 0 5 9	59 0 54·0
Modern with expectant	Macafee (1945) Grant (1955)	0 57 0 00	23 5 9 9

Therefore, we felt it was safe to allow the patient to go home from hospital when placenta prævia had been excluded radiographically In a woman who has had antepartum hæmorrhage, the os should be inspected through a speculum after a week's rest, to exclude lesions of the cervix, she is then allowed to return home We have latterly adopted this procedure without regrets Chassar Moir (1956) supports this view

> " If in a case of antepartum hæmorrhage a low implantation of the placenta can be excluded, the patient can be spared the necessity of a vaginal examination, and can, after a week's rest, be allowed to return home without fear of renewed, violent hæmorrhage "

Summary

Radiographic evidence of the placenta in the upper uterine segment is highly accurate A single lateral radiograph of the uterus after 34 weeks' gestation is enough to exclude placenta prævia

Of 107 patients investigated by direct and indirect placentography (soft-tissue radiographs and measurement of the displacement of the fœtal head), 17 had placenta prævia, which was diagnosed correctly in 12 cases and suspected in 2

A lateral uterine radiograph requires no special skill or equipment, but transillumination of the film by a 100-watt bulb may be needed to detect the anterior wall of the uterus and the abdomen One such radiograph is compatible with good obstetric standards, irradiation to the fœtus and mother is minimal, film costs are reduced, and fœtal abnormalities may also be detected

X-ray location of the placenta in the upper uterine segment relieves the patient's anxieties for she can be sent home without fear of violent hæmorrhage, and hospital beds are not filled unnecessarily

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Preliminary Communications

NUCLEAR CHANGES IN ORAL EPITHELIUM IN PERNICIOUS ANÆMIA

EPITHELIAL atrophy of the tongue is said to occur in about 70% of cases of pernicious anæmia,[1] but little study has been made of the response of the tongue to specific treatment An attempt was therefore made to examine cytological material from the tongue, but preparations were unsatisfactory, probably because of the heavy keratinisation of the epithelium Examination of oral mucosa from the inside of the cheek has, however, proved more satisfactory and a study of nuclear abnormalities and changes in size has been made in patients with pernicious anæmia

Changes in gastric columnar cells in pernicious anæmia have been reported by Massey and Rubin,[2] while desquamated squamous cells present in gastric aspirate were examined by Graham and Rheault [3] They measured the greatest cytoplasmic diameter and found it increased Recently Boen [4] has described nuclear changes in exfoliated squamous cells from the mouth and has made comparative measurements of the longer axis of the nucleus In seven out of his ten patients with pernicious anæmia, enlarged squamous-cell nuclei were seen and the nuclei were restored towards normality by specific treatment The three cases with relatively normal nuclei were excluded from this comparison Morphological abnormalities of the nucleus, and in particular a reticulated chromatin structure, were found to disappear during treatment A series of normal controls matched according to age were also examined by Boen

In the present study, preparations of oral mucosa have been taken by scraping the inside of the cheek with a microscope slide Thirty-nine cases of pernicious anæmia have been studied in this way and similar changes of nuclear size and morphology noted Twenty-five of these cases have been re-examined later at periods varying from 2 to 32 months from the date when they were first diagnosed and treated, and in twenty-two of these there has been evidence of diminution in nuclear size In all cases 100 nuclei have been measured in both longer and shorter axes, and the averages of these measurements used for comparison

Material from ninety-five normal controls of varying ages has also been examined by the same technique By relating nuclear size to age (see figure), a surprising increase of the shorter axes of the nuclei becomes evident The effect is obvious only over the age of 60, and if normal controls of 60 years and over be compared with the rest a significant difference arises ($P<0\ 05$) For this reason, the results from cases of pernicious anæmia have been compared for each axis within two age-groups—35–59 years, and 60 years and over

TABLE I—MEAN AXIS MEASUREMENTS IN PERNICIOUS ANÆMIA AND CONTROLS

Cases	Age range	No	Mean and standard error		Standard deviation	
			Longer axis	Shorter axis	Longer axis	Shorter axis
Pernicious anæmia	35–59	17	12 127± 293	9 496± 231	±1 210	±0 953
	60+	22	12 342± 202	9 618± 203	±0 945	±0 950
Normal controls	< 35	33	11 709± 117	8 435± 127	±0 670	±0 728
	35–59	41	11 636± 091	8 558± 108	±0 582	±0 694
	60+	21	11 920± 112	8 930± 123	±0 512	±0 561

TABLE II—PERNICIOUS ANÆMIA AND CONTROLS ANALYSIS OF RESULTS

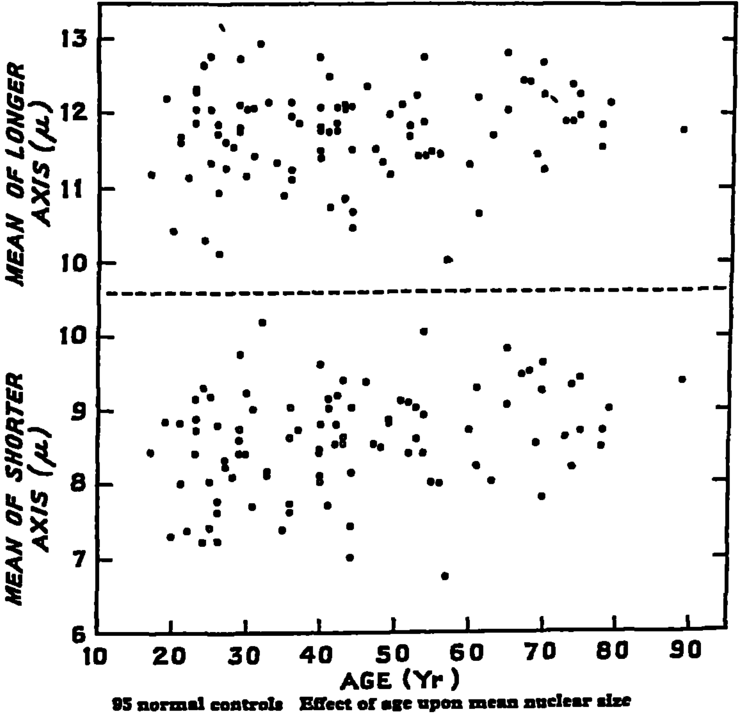
Age range	t		P	
	Longer axis	Shorter axis	Longer axis	Shorter axis
35–59	1 60	3 68	not signif	< 0 001
60+	1 83	2 91	not signif	< 0 01

When all thirty-nine cases of pernicious anæmia, including those few with relatively normal nuclear size, are compared with their controls in the two age-groups, it becomes apparent that measurements in both axes in pernicious anæmia are greater than in controls (table I) This apparent increase in size in the pernicious anæmia nuclei falls just short of significance level for the longer axis, but is highly significant for the shorter (table II) The degree of significance is less for the over-60 age-group and this appears to be due to the effect of age upon the normal controls

Ten cases of normocytic normochromic anæmia have also been examined and the nuclear size has been found to lie within the normal range Groups of controls with achlorhydria and oral sepsis show no significant departure from the normal

One patient with a smooth tongue in the absence of anæmia, with a normal level of serum-iron, and with free acid in the stomach was found to have abnormally large squamous-cell nuclei which reverted towards normal with oral administration of vitamin-B complex Results in iron deficiency are being studied

One may conclude therefore that squamous-cell nuclei from the mouth are abnormally large, particularly in the shorter axis, in pernicious anæmia, and that they revert



95 normal controls Effect of age upon mean nuclear size

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owards normal with treatment In the elderly the nuclei end to be larger It appears that megaloblastic anæmia nay not be the only condition in which abnormally large uclei are seen

I should like to thank Prof C B Perry, Dr W A. Gillespie, and r F G Bolton for much advice and encouragement, and Miss . H L Duncan for statistical help The work is being done with he aid of a grant from the governors of the United Bristol Hospitals

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CLINICAL DEXTRAN FOR ACUTE EPISODES IN PAROXYSMAL NOCTURNAL HÆMOGLOBINURIA

IN 1955, Pillemer[1] described properdin as a natural immune property of serum, and later Hinz et al [2] brought forward evidence that the hæmolysis of the red blood-cells in paroxysmal nocturnal hæmoglobinuria was due to the interaction of properdin with the stroma of the intact red cells

One of us (F S) found that, in some healthy persons of blood-group O, the properdin titre differed according to the temperature at which the red cells are separated from the serum. In these people, if whole defibrinated blood was used and the mixture allowed to stand at 0°C $1^1/_2$ hours, the properdin titre was altered, and in some cases a much lower titre was obtained than when the serum was separated from the blood at 37°C immediately after it had been collected If, before the whole defibrinated blood was cooled to 0°C, certain substances, including clinical dextran, were added in suitable concentration, the subsequent cooling of the mixture to 0°C did not decrease the properdin titre

Dextran was, to some extent, anticomplementary and was also one of several substances which, in certain concentrations, prevented the activity, in most cases, of any previously existing cold incomplete anti-H antibody There are many explanations of the interference with the properdin content of the serum associated with the incubation of group-O blood with its own cells at 0°C in these cases, one is the possibility that it is associated with the union of cold incomplete anti-H antibody with the red cells at this temperature This relationship is being worked out, and further details will be published later

These laboratory investigations suggested that clinical dextran might be valuable for the control of the acute episodes of paroxysmal nocturnal hæmoglobinuria, so it was tried in two cases

Case 1 —A man with typical paroxysmal nocturnal hæmoglobinuria had been under observation in the department of hæmatology for $2^1/_2$ years and occasionally had to be admitted because of acute episodes of hæmoglobinuria that sharply lowered his hæmoglobin level Such episodes were usually treated by blood-transfusions, but in one of them infusions of clinical dextran were substituted for blood-transfusion The dextran infusions were effective, and the hæmoglobinuria ceased, but it recurred some time after the dextran infusion had stopped

Case 2 —A married woman with typical paroxysmal nocturnal hæmoglobinuria was under the care of Dr M L Thomson of Salford Royal Hospital She had been under observation for many years, and the present attack of hæmoglobinuria had lasted 6 weeks She was admitted to hospital, and her hæmoglobin was 7 5 g per 100 ml Clinical dextran 1 litre was infused, and next morning her urine contained no hæmoglobin Next day she had a transfusion of packed washed cells, which was followed by pyrexia and a rigor, and some hæmoglobinuria returned, with failure of the hæmoglobin to increase by the expected amount. On the day after the transfusion the patient was infused with clinical dextran 500 ml, and this was followed by considerable diminution in the hæmoglobinuria, which in two or three days disappeared altogether Her hæmoglobin on leaving the hospital was 8 g per 100 ml When she attended the outpatient department ten days later, her hæmoglobin was 9 5 g per 100 ml, and there had been no recurrence of hæmoglobinuria

It is, of course, well known that hæmoglobinuria developing in paroxysmal nocturnal hæmoglobinuria will sometimes stop spontaneously The results we have obtained are suggestive, but it is clear that the treatment could be tried on more patients Since individual physicians rarely see more than one or two cases, we are publishing this report at an early stage in the hope that others will be interested in trying the infusion of dextran during an acute episode of paroxysmal nocturnal hæmoglobinuria

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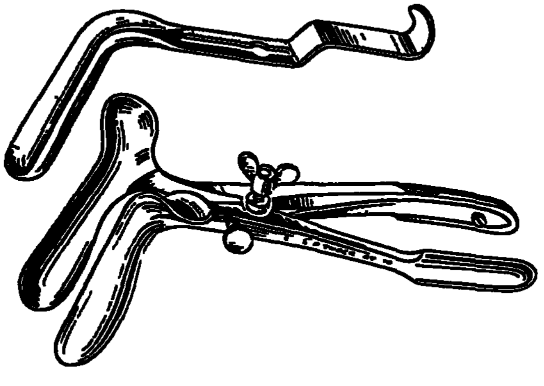
New Inventions

THREE-BLADED SPECULUM FOR INTERNAL ANAL SPHINCTEROTOMY

THE treatment of chronic anal fissures by deliberate division of the internal sphincter is the method favoured by an increasing number of surgeons For its accurate performance a speculum is required which separates the anal margins and exposes the posterior wall of the anal canal for incision Some variety of bivalve speculum is commonly used for this purpose, but in my experience this has not always given entirely satisfactory access, and I have recently designed a three-bladed speculum which I think has certain advantages (see figure)

The instrument has two main lateral blades, to each of which a handle is attached at one end almost at right-angles to the axis of the blade The two handles are connected at a pivot $1^1/_2$ inches from the blades Normally the two handles are kept apart by a spring which brings the blades of the instrument into firm apposition The coopted blades form a smooth and more or less cylindrical mass of metal which has a conical tip like a fairly narrow tubular proctoscope and



is easily introduced into the anal canal Once the speculum is in position with its handles lying anteriorly, the blades are separated by approximating the handles gradually against the resistance of the spring When the required degree of separation has been achieved it can be maintained by tightening a distraction screw

In many cases this manœuvre by itself gives an excellent view of the posterior anal wall, sufficient for sphincterotomy In some patients, however, internal hæmorrhoids are present in addition to the fissure, and the right anterior pile tends to bulge into the lumen between the front edges of the lateral blades To overcome this difficulty a third (anterior) blade has been devised to retract this wall strongly forwards It is attached by a handle to the pivot of the speculum, and when in place it always provides untrammelled access to the posterior wall and its fissure

Another feature of this speculum is that each of its three blades is slightly waisted near its external end When the expanded instrument is in situ, the anal sphincters grip this waist so that, by downward traction in an axial direction, the surgeon can to some extent draw the internal sphincter out of the anal canal and render its distal portion specially prominent for division

Though this speculum was designed primarily for internal sphincterotomy, it also affords ideal exposure for other fairly common operations—e g , removal of hypertrophied anal papillæ under local anæsthesia in the outpatient department, and for diathermy of benign tumours of the extreme lower end of the rectum It is also admirable for submucosal hæmorrhoidectomy according to the technique advocated by Parks [1]

The speculum was made to my specification by Messrs Charles F Thackray, of Leeds

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Reviews of Books

The Extra Pharmacopœia

24th ed Vol I London Pharmaceutical Press 1958 Pp 1695 £3 5*s*

IT is seventy-five years since the first edition of Dr Martindale's *Extra Pharmacopœia* appeared, and the fact that it is now in its 24th edition testifies to the esteem in which it is held the world over The many new remedies introduced in the past six years have made the new edition much bulkier than any of its predecessors Because " Martindale " is a book of reference and not a textbook, information about older drugs, even though now seldom used, must be retained Some sections have indeed been pruned, but the omissions are few compared with the additions The main titles of drugs are now in English instead of Latin—a change that conforms with the practice now followed in the *B P* and *B P C* It is perhaps unfortunate—yet unavoidable—that most of the text was compiled with reference to the 1953 *B P* and 1955 *Addendum*, but a section on the changes brought about by the *B P 1958* is included at the beginning of the book It is pleasing to note that the abstracts of original papers, which are such a feature of " Martindale ", are now more critically selected, and this also applies to the therapeutic index, which no longer includes many references of historical interest only The special section on antibiotics introduced in the last edition has been expanded, and there is a valuable new section on radioactive isotopes

The text is as up to date as can be, and the editors and their collaborators are to be congratulated on a large task ably fulfilled

Atlas of Systematic Human Anatomy

Vol III GERHARD WOLF-HEIDEGGER, M D , PH D , professor of anatomy and prosector at the Anatomical Institute of the University of Basle Edinburgh and London E & S Livingstone 1957 Pp 167 55*s*

THOSE who appreciated the excellence of the first volume of Professor Wolf-Heidegger's atlas will not be disappointed in the new one, which illustrates the nervous, vascular, and lymphatic systems

Foreword and preface are in English, the section headings and title captions are in German, which is no real disadvantage to those who do not read German since the reading matter is almost entirely distributed in labels explaining the figures, which are couched in Latin No doubt some readers will be able to translate these terms into English anatomical vernacular with ease, but Prof G A G Mitchell's assumption, in the foreword, that " Latin terms are understood and employed by the majority of medical men " is overoptimistic There has been a big decline in the Latinity of medicine in the past decade or two, and it is doubtful whether students or graduates who cannot distinguish " ilium " from " ileum ", or appreciate philologically the desirability of " dorsal ", will be able to disentangle the nominatives and genitives of " confluens sinuum " or " R radicularis r spinalis a vertebralis " The section on the brain is excellent, and the draughtsmanship of the figures illustrating vessels and lymphatics is of the highest order, though many of them seem overburdened with details and labels

Just how useful are such atlases, however excellent in execution? Most professional anatomists would be at once attracted by this volume, and perhaps it should be in their departments But such atlases are too expensive for students or graduates preparing for higher qualifications, and anyway both would be better advised, like their clinical elders, to learn or revise by direct experience of living or cadaveric structure The draughtsmanship, the scholarship, the printing, are, as in some other atlases, superb, but is the effort justified?

Forensic Medicine (London Edward Arnold 1958 Pp 340 30*s*)—The medical student usually prefers a short textbook, and here he is lucky, for Dr Keith Simpson's is not only short but one of the most readable and informative of all books designed for medical students We have no hesitation in recommending it Many of the changes in the new edition have been made necessary by new laws and regulations or recently discovered drugs for which " the doctor must be on the *qui vive*—or rather *qui mort* " There are several new illustrations of good quality, but many of the familiar ones remain

Recent Advances in Obstetrics and Gynæcology (9th ed London J & A Churchill 1958 Pp 348 38*s*)—A new edition of Mr Aleck Bourne and Mr Leslie Williams' book appears every five years or so, and each is probably more valuable and popular than its predecessors The authors have by now, so to speak, got into their stride They try not to record indiscriminately all the latest discoveries, but rather to present a summary, and accompanying criticism, of consolidated advances They succeed admirably The new volume includes chapters on acute renal failure, anæmia in pregnancy (by L Steingold), coagulation defects, and intravascular thrombosis, and all are very good Purely clinical are those dealing with the present knowledge of uterine cancer and that entitled Changing Trends in Obstetrics, in which is to be found a faint hint of things to come Under antenatal care are considered anæmia, diabetes, abnormal weight gain, and the dangers of radiology—no mention of the mechanistic troubles that occupied so prominent a place in the past Perhaps in a future edition the whole chapter on antenatal care will be concerned with the importance of securing and maintaining the health of the pregnant woman The authors are so broad-minded as to present all sides of any debatable subject and so experienced as to be dogmatic when dogma is desirable The book is well illustrated and so delightfully written that the authors must plainly have enjoyed their task This excellent production is probably the best of the series

THE LANCET
LONDON 19 APRIL 1958

Influenza 1889 and 1957

It is nearly a year since the influenza epidemic which began in China reached Hong Kong and Singapore From the beginning this epidemic aroused more than ordinary public interest, because of the predictions (accurate in the event) that the Asian virus would spread throughout the world, and because of the rush to prepare vaccine with the new virus in advance of the epidemic wave But there was another reason for public interest and for some disquiet In the minds of many people epidemic influenza is forever associated with the pandemic of 1918–19, when influenza is estimated to have caused nearly 20 million deaths, and echoes of this were awakened by a series of most unusual laboratory findings

Very early in the epidemic Meyer et al[1] showed that sera taken from people before the epidemic reached the U S A were virtually devoid of antibodies to the Asian virus This finding was an important factor in predicting a high incidence of influenza in the autumn of 1957, and it also allowed the conclusion that viruses like the Asian virus were newcomers to the population Shortly afterwards, however, Mulder[2] reported briefly that some of the people in Holland aged 80–90 had small amounts of antibody to the Asian virus Since antibody was known to be rare or absent in younger people, Mulder suggested that the antibody in these old people might have resulted from infection during their childhood with a virus closely related to the Asian virus These childhood infections could have corresponded in time with the world-wide influenza epidemic of 1889, which suggests a most interesting hypothesis —that after the 1889 epidemic the virus remained dormant, possibly in an animal reservoir, until it reappeared in 1957 This week we publish three important papers describing evidence for and against this hypothesis The arguments are to some extent concerned with technical laboratory findings, but this is not just an academic problem If Mulder's hypothesis is correct we have to ask ourselves what has happened to the virus of the 1918–19 pandemic Will it, too, reappear, and if so will it be as virulent as before?

Professor Mulder and Dr Masurel (p 810) describe the laboratory findings concerning antibodies to the Asian virus and outline the hypothesis concerning the relation to the 1889 epidemic As a first step sera were collected from people of different ages in Holland before signs of epidemic spread of the virus had appeared, and through the World Health Organisation other laboratories were asked to collaborate in this investigation The sera were examined individually for antibody to Asian virus by the hæmagglutination-inhibition test, the sera being pre-treated with a filtrate of *Vibrio choleræ* to remove normal inhibitors of agglutination Positive hæmagglutination-inhibition titres were found in 52 of 1256 sera examined The proportion of positive titres increased with age, being in the range 1–2% in the 30–69 age-group, 5% in the 70–79 group, and 22% in the 80–89 group The same sera showed antibody by an independent test (the mouse-protection test), and there is little doubt that both tests were measuring true antibody The results of complement-fixation tests with the same sera make it clear that the antibody had not resulted from recent infection with Asian viruses The problem then is what is the significance of the antibody and of its age-distribution? Mulder and Masurel conclude that the human race was in contact with the dominant hæmagglutinating antigen of the Asian virus in the last quarter of the 19th century, and that the 1957 epidemic probably represents a repetition of the 1889 epidemic We are reminded that the 1889 epidemic probably originated in Central Asia and perhaps in China Their conclusion is based, however, on the age-distribution of the antibody and on the evidence of Davenport et al[3] that, generally speaking, the age-distribution of the serum antibodies to different antigenic varieties of influenza virus reflects the prevailing viruses during the childhood of the people of the different age-groups Thus Mulder and Masurel draw an analogy between antibodies to the Asian and swine influenza viruses, there is good evidence that the latter were prevalent at the time of the 1918–19 epidemic[3-5] The conclusions of Mulder and Masurel are supported by Davenport,[6] who found that in Michigan, U S A, antibody detectable by complement-fixation with Asian-virus antigen was not present in persons below the age of 30, but was usually present at low levels in those over 30

The other side of the argument is set out by Dr Clarke and her colleagues (p 814) They found that of 154 sera collected in England before July, 1957, only 6 gave hæmagglutination-inhibiting antibody to the Asian virus, these 6 sera were from persons of various ages, and only 1 of 19 persons aged 80 or more showed antibody Sera collected in 1955 and pooled according to age in 2-year age-groups, between the ages of 2 and 78, were uniformly negative for Asian-virus antibody This was in striking contrast to the postepidemic experience 44% of 637 sera taken last November had antibody—a remarkable tribute to the powers of spread of the virus in this country The findings of Clarke et al do not support the idea that Asian antibody in pre-epidemic sera was present in any particular age-group In addition, Clarke et al examined sera from 168 young people, mostly aged 18–25, who were vaccinated in 1955 and 1956 with vaccine which did not contain Asian virus When the same sera, which had been kept stored, were subsequently tested 5% were found to have had a rise in antibody to the Asian virus Essentially the same finding was noted by Mulder and Masurel, who report that of 323 people of various ages vaccinated in 1956 and early 1957 9% subsequently had antibody to the Asian virus in their sera The only obvious explanation is that the Asian virus is not so completely unrelated to previous influenza viruses as is suggested by direct cross-testing with animal sera in the hæmagglutination-inhibition test, and this conclusion is strikingly confirmed in the paper by Dr Henle and his colleagues (p 818) They found that by means of a complement-fixation test which they have recently developed, and which uses the V (or viral-specific) antigen extracted from the virus, it was possible to demonstrate antigenic relationships between the Asian virus and three viruses isolated in 1933, 1951, and 1953 This cryptic relationship had not been suspected from the results of direct hæmagglutination-inhibition tests, and it may explain why antibody to Asian virus can develop in young people vaccinated with influenza viruses apparently quite different from the Asian virus

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[1] Meyer, M H Jr, Hilleman, M R, Miesse, M L Crawford, J P, Bankhead A S *Proc Soc exp Biol*, N Y 1957, 95, 609

[2] Mulder, J *Lancet*, 1957, ii, 334

[3] Davenport F M, Hennessy, A V, Francis, T, Jr *J exp Med* 1953 98, 641

[4] Laidlaw, P P *Lancet*, 1935, i, 1118

[5] Shope, R E *J exp Med* 1936 63, 669

[6] Davenport, F M *Publ Hlth Rep*, *Wash.* 1958, 73, 133

How then are we to account for the fact that before the Asian epidemic those with Asian antibody were concentrated in the older age-groups? A hint is given in the report by Dr Holland and his colleagues (p 820) They found that Asian virus given as a single dose of vaccine induced a very poor antibody response By contrast, the same dose of vaccine given to people previously infected with Asian virus or to people who had previously been given one dose of Asian-virus vaccine led to a good antibody response By extending this finding we could postulate that repeated infection of people over many years with viruses containing a cryptic "Asian" antigen could have induced Asian antibody, whereas single infections would not have done so, and it is among older people that repeated infections of this kind would be expected to occur This hypothesis is strengthened by the finding of Henle et al that in guineapigs given repeated intranasal inoculations of different viruses a very specific antibody response gradually broadened to embrace more and more viruses, including the Asian virus, which had not been included among the viruses inoculated

This reasoning is in line with that of Hilleman et al,[7] who have studied the distribution of antibody to Asian virus in pre-epidemic sera among different age-groups in the population near Washington They were concerned with one technical aspect of the hæmagglutination-inhibition test—that treating the sera with *Vibrio choleræ* filtrate may destroy traces of antibody along with normal inhibitors of agglutination When they used a strain of virus which was not sensitive to these normal inhibitors, and thus were able to avoid using *Vibrio choleræ* filtrate, they found that the age-distribution of Asian-virus antibody was not sharply confined to older people, there were low antibody levels in people aged 20–40, and the levels rose gradually to a maximum in people aged 50–59 and remained the same thereafter This technical factor may explain the differences in age-distribution found by different investigators But Hilleman et al also show, as did Henle et al by an independent technique, that the distribution of antibody to older strains is not confined to people who were alive at the time when these strains were prevalent The same finding was noted in the sera of Nigerians by Isaacs,[8] who concluded that antibody to an influenza virus could not be taken as evidence of infection with that particular virus, but might result from infection with strains with which it shared minor antigens Thus it seems that the antibody spectrum in the population does not sharply reflect previous experience with influenza viruses, the mirror images are blurred, and we should beware of overestimating our powers of focusing them

There is a practical aspect of this controversy in connection with influenza vaccines Davenport,[6] who has accepted the idea that the 1957 virus is very similar to the 1889 virus, takes this conclusion as evidence for his belief that influenza viruses contain a finite number of antigens and that the viruses of the past will reappear as immunity to them in the population gradually recedes Davenport believes that if the number of antigens in the influenza virus is relatively small it will be possible to prepare a polyvalent vaccine which would protect against all the possible antigenic forms that the influenza viruses could assume Alternatively, if influenza viruses can mutate freely there is little to be gained by this approach to influenza vaccination, and vaccines should incorporate up-to-date viruses and thus at least take account of the most recent major antigenic change of the virus As with most theoretical arguments, theories are of little account compared with facts The only way to settle this controversy is to compare the protective power of polyvalent vaccines made from older strains with vaccine made from a more up-to-date strain This was in fact done in the recent epidemic In this country the Medical Research Council's Committee on Influenza Vaccine Trials[9] found in a carefully controlled trial that a polyvalent vaccine containing three older influenza-A viruses gave no protection, whereas a monovalent vaccine containing the Asian virus gave approximately 67% protection In a similar type of trial at Great Lakes Naval Training Centre in the U S A, a polyvalent vaccine without Asian virus is reported to have caused slight protection, estimated as 45%, which was less than that found with adequate doses of monovalent Asian vaccine[10] Experience in these trials and in previous ones in 1947–48 seems to warrant the conclusion that when a major antigenic change in the influenza virus has taken place vaccines made with older strains are unlikely to give a useful degree of protection, whereas vaccines made with the epidemic virus can give reasonable (although by no means complete) protection On the other hand, when slight antigenic changes in the virus take place there is little to be gained by using the most up-to-date virus, and the use of recent and related viruses should be just as effective

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[7] Hilleman, M R, Flatley, F J, Anderson S A, Luecking, M L, Levinson, D J *New Engl J Med* (in the press)

[8] Isaacs, A *J Hyg, Camb* 1957, 55, 485

[9] Medical Research Council Committee on Influenza and Other Respiratory Virus Vaccines *Brit Med J* Feb 22, 1958 p 415

[10] Commission on Influenza of the Armed Forces Epidemiological Board *J Amer med Ass* 1957, 165, 2055

As to the whereabouts of the 1918–19 virus and whether something similar to the pandemic of that time will ever recur, we are as much in the dark as before But one thing is clear—there is less excuse than ever for relaxing our watch on the influenza viruses

Cancer of the Large Bowel

With scrupulous attention to history and examination the diagnosis of cancer in the large bowel should not often be missed From an analysis of 1023 cases in the U S A , Postlethwait et al [1] have found abdominal pain and change in bowel habit or character of the stool to be the predominant symptoms, and Muir [2] reports similar findings in 714 patients in this country But there is an odd discrepancy between the two series In the American cases bleeding was the commonest symptom of rectal cancer and the second commonest of cancer elsewhere in the large bowel In the British cases bleeding was one of the main symptoms in less than 10% of patients with neoplasms in right or left colon, in 30% (fourth in order of precedence) of those with neoplasms in the sigmoid, and in 66% (second place to "bowel complaint") when the rectum was involved Perhaps cancer education has caused American patients to become more observant and less phlegmatic than the British

It is an odd paradox that investigations can sometimes put us off the diagnostic scent Many patients now present themselves with vague abdominal symptoms requiring investigation to exclude organic disease, and a negative result may wrongly be given greater weight than the evidence of symptoms or signs Ramsay [3] has drawn attention to this danger in six years at the Gordon Hospital, London, 2325 barium enemas were undertaken and 151 patients with colonic cancer were treated Of these 151, 75 had been radiographed, and a negative report had been given in 10, leading to delay in diagnosis in 7—despite sufficient clinical evidence to warrant laparotomy A history or symptom suggesting carcinoma should take priority over a normal radiographic appearance, and radiographic evidence should be allowed to outweigh clinical evidence only when X rays show positive changes

Recurrence at the suture-line after resection remains a problem [4] The mechanism is uncertain; Goligher et al [5] and Cole [6] believe that implantation of malignant cells at the time of operation is an important cause Certainly such cells do exfoliate from the lesion —a process presumably encouraged by operative manipulation Indeed Pomeranz and Garlock [7] suggest that recurrences are brought about in the wound and peritoneal cavity by exfoliated cells transported there on the surgeon's gloves Goligher et al , who were concerned with sphincter-saving resections for growths of rectum or rectosigmoid, thought that possibly only half of 23 recurrences could be explained on the implantation hypothesis, others being due to fresh lesions or incomplete removal of the original one Likewise of 108 recurrences seen at the Mayo Clinic after anterior resection, 12 were attributable to incomplete excision, and 7 to further neoplastic degeneration in a potentially malignant mucosa [8] In the rest (less 10 cases in which the original specimen could not be examined) there was no clear explanation other than by the implantation theory, and Lofgren et al [8] observe that this would explain why recurrence at the suture-line is independent of lymph-gland metastasis and takes place soon after operation The Mayo Clinic series were compared with a control group of 102 patients who survived anterior resection for five years, no significant features could be found on examination of the specimens from the two groups Cole and Southwick [9] have found that malignant cells can be detected growing inside the veins at the tumour site or close by, and that such cells appear in a venous perfusate of the lesion, thus this type of recurrence may be caused as much by local venous invasion as by the intramural and pericolic retrograde lymphatic spread suggested by Beal and Cornell,[10] in whose series lymph-node involvement and invasion of the entire colonic wall was common at the primary lesion—in contrast to experience at the Mayo Clinic [8] In addition to the technical precautions suggested by Cole to minimise the possibility of implantation (namely, isolating the growth with tape ligatures placed round the bowel) and by Pomeranz and Garlock (who cover the surface of the lesion), Beal and Cornell suggest that the limits of resection should be extended

In 19 of Beal and Cornell's 21 cases of recurrence after resection in 140 patients, the original growth was on the left side Such a preponderance of recurrence, not noted in the other series, could be explained by the fact that this is the common site for polyps, the inference then being either that recurrence is due to small polyps at the suture-line not observed at operation (in 1 postoperative death a residual papilloma was found adjacent to the anastomosis) or that polyps developing in the natural course of events cause the primary lesion and develop again in the predisposed mucosa on either side of the anastomosis But opinions are divided as to whether small papillomas are sinister, Grinnell [11] maintains that they are not if the lesion is less than 1 cm in diameter, while Weingarten and Turell report malignancy in polyps as small as 3 mm [12] Figiel et al ,[13] who can demonstrate small lesions of the colon with greater ease by their high-voltage " spot-compression " technique, suggest that small asymptomatic polyps beyond the range of the sigmoidoscope do not require extirpation provided the patient is kept under surveillance This raises the important issue whether all colonic polyps—adenomatous or papillomatous, large or small, on the right side or the left—should be regarded as premalignant and treated accordingly Correlation between the incidence of polyps and that of cancer is not immediately obvious, in 50,000 routine proctosigmoidoscopic examinations Portes and Majarakis[14] found polyps in 7 9%, cancer in 0 685% This question is important in management, for already Lillehei and Wangensteen[15] have advocated total or subtotal colectomy for cancer distal to the hepatic flexure and similarly for right-side lesions provided no more than 20 cm of ileum has to be removed (if more is taken, then the sigmoid may need to be retained in order to avoid diarrhœa following ileoproctostomy) Further support for this approach has come from Teicher and Abrahams[16], but Grinnell,[11] after studying 1335 cases with adenomas and papillomas, found that only 1 in 67 might have benefited from such major procedures, and 8 out of 66 with multiple cancers would have similarly benefited—this representing 0 73% of 1083 cancer resections during the period under review Wakeley and Graves[17] remark that simple removal of a papilloma that is proved histologically to be carcinomatous is sometimes not followed by recurrence Turnbull,[18] who reports on 86 patients treated for carcinoma in polyps of the colon and rectum, considers that no hard-and-fast rules can be set forth for their treatment

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[1] Postlethwait, R W , Adamson, J E , Hart, D *Surg Gynec Obstet* 1958, 106 288

[2] Muir, E G *Brit J Surg* 1956 44 1

[3] Ramsay, G S *ibid* 1956, 43, 576

[4] See *Lancet* 1954, ii, 79, *ibid* 1956, i, 944

[5] Goligher, J C , Dukes, C E , Bussey, H J R *Brit J Surg* 1951, 39, 199

[6] Cole, W H *Arch Surg* 1952 65 264

[7] Pomeranz A A , Garlock, J H *J Amer med Ass* 1955, 158, 1434

[8] Lofgren, E P , Waugh, J M , Dockerty, M B *Arch Surg* 1957, 74, 825

[9] Cole, W H , Southwick, H W *J Amer med Ass* 1954, 155, 154

[10] Beal, J M , Cornell, G N *Ann Surg* 1956, 143, 1

[11] Grinnell, R S *Surg Gynec Obstet* 1958, 106, 288

[12] Weingarten M , Turell, R *J Amer med Ass* 1952, 149 1467

[13] Figiel, S T , Figiel, L S , Rush, D K *ibid* 1958, 166, 1269

Cerebral Palsy

Cerebral palsy is a topic that bristles with difficulties, and one of the sharpest bristles is the nosological The term includes a variety of lesions of the brain, each with various origins and various clinical manifestations It has some merit in that patients with cerebral palsy (which may be defined as a congenital motor deficiency that is not progressive) tend to have certain needs in common, but it has drawbacks too, in that the needs of children with cerebral palsy, so defined, differ from case to case, and overlap those of some children with acquired lesions (e g, from encephalitis early in life) who present a similar clinical picture Not only does the nature and severity of the motor defect vary widely, but some children have also severe mental defect, others little or none, some have fits, some athetosis, others neither, about 20% have severe hearing defects, which may not be detected until audiometry is done[19] and may be misdiagnosed as mental defect, and some (as many as 50%) have impaired sensation, the importance of which is just being recognised—it is of little use to train a child to use a limb that he cannot feel[20] Moreover, family circumstances (the income and intelligence of the parents, the presence of siblings, and the geographical situation of the home) partly determine the needs of individual patients "Go in fear of the abstract" was Ezra Pound's advice to poets "go in fear of the general" might be a good motto for doctors, especially where the particular circumstances and needs range as widely as they do in cerebral palsy

There is no cure for cerebral palsy, the damage to the brain, or failure in its development, cannot be made good But much can be done to help muscle development and coordination, by making the most of the power that remains, and perhaps by bringing to the surface dormant reflex patterns that are not used by people with undamaged brains[21] Drug treatment may help K H Sparup, in a letter,[22] and Alan Moncrieff, in a lecture to the British Council for the Welfare of Spastics,[20] have referred to the varying results when primidone is given for athetosis associated with cerebral palsy, and meprobamate for spasticity or athetosis There is also a place for operation in some cases hemispherectomy has abolished fits and temper tantrums without making the paralysis worse[23 24] There is some hope that athetosis may be improved by a method, mentioned by Professor Moncrieff, of injecting alcohol, with or without celloidin, into the corpus striatum, but such techniques are still being developed and tested, and though it is of great value to remove the handicap that athetosis or epilepsy adds to the paralysis, the chief disability remains

It is very important, then, that the child with cerebral palsy should have the best possible treatment for his motor defect, this treatment is educative, and to be effective must begin soon The aim, at least in some centres, is to make as many as possible of these children capable of going to normal schools at school age,[25] which means that the diagnosis must be reached as early as possible—and that, once this has been done, treatment must not be delayed At present the delay is often too long Dr Lawson, in his account (p 840) of the cerebral-palsy unit at Queen Mary's Hospital, Carshalton, says that only a tenth of the patients were referred in the first eighteen months of life, and a third were over the age of 5 years, while Ingram[26] found that only 4 of 79 spastic children were correctly diagnosed in the first year Early diagnosis is far from easy Moncrieff mentions such slight signs as "a little undue flabbiness, a rather suspicious rolling of the head there is often a suspicious sort of rigidity present", and he refers to the spastic tone of the spastic child, contrasted with the plastic tone of the athetoid child—"there is a feeling about the movements which those who work with these children know about, which, as we have found, is difficult to explain to other people" Those in the best position to detect cerebral palsy early are child-welfare workers and the family doctors who take a special interest in babies, who are most likely to detect slight differences from the normal Ideally all babies should be examined periodically by a doctor, and such examination is definitely necessary wherever there has been any complication of pregnancy, labour, or the neonatal

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14 Portes, C, Majarakis, J D *ibid* 1957, 163 411
15 Lillehei, R C, Wangensteen, O *ibid* 1955, 158, 163
16 Teicher, I, Abrahams, J I *Surg Gynec Obstet* 1956, 103, 136
17 Wakeley C, Graves, F T *Lancet*, Feb 15 1958, p 329
18 Turnbull, R B *Dis Colon Rectum*, 1958, 1, 44
19 Fisch, L *Lancet*, 1955, ii, 370
20 Moncrieff, A Cerebral Palsy Today an address to the British Council for the Welfare of Spastics 13, Suffolk Street, Haymarket, London, S W 1 1957 Pp 15 1*s* 6*d*
21 *Lancet*, 1954, ii, 746
22 Sparup, K H *ibid* 1957, ii, 807
23 Krynau, R A *S Afr med J* 1950 24, 539
24 McKissock W *Proc R Soc Med* 1953 46, 431
25 *Lancet*, 1954 i 90
26 Ingram, T T S *Arch dis Childh* 1955, 30, 244

period. But making a firm diagnosis requires a good deal of experience of cerebral palsy: indeed, Dr Lawson holds that about 50 new cases must be seen every year if facility is to be acquired in diagnosis and treatment. The work of such a special diagnostic unit includes estimation of intelligence as well as of motor function, in the children with cerebral palsy the prognosis and treatment depend in part on the mental ability. Those with normal intelligence can often learn to use their motor system in such a way that no deformity develops.[27] It is of course far from easy to estimate intelligence in infants, but some useful tests are given by Mrs Collis.[28]

When the diagnosis has been made, treatment must begin at once, to prevent abnormalities of function and structure. But in each case the physician must decide, not only the treatment given, but also who is to give it, and where. In the article we published last week Dr Ellis estimates the part that individuals and voluntary agencies must play, and the responsibility of society in providing the range of institutions needed. Surveying the provision made for 133 cerebral-palsy children of school age in three local-authority areas, he contrasts it with the provision he regards as desirable. He would have fewer patients attending normal schools because many had "specific learning difficulties or were so backward that they needed more individual help than their teachers could afford to give them." He thinks that a much larger proportion should attend schools for the educationally subnormal—of which there is a general shortage. About a third, he believes, should be in schools or occupation centres specially established for children with cerebral palsy. Dr Lawson suggests that children with cerebral palsy should go to the type of school most suitable in each individual case, but be grouped in certain schools in a wide area: this would ease cooperation between the schools and the cerebral-palsy service. Both Dr Lawson and Dr Ellis emphasise the importance of parents being instructed and taking part constantly in the treatment when the child is living at home.

Even in a closely packed community such as ours there are geographical difficulties. At Dr Lawson's clinic, 40% of the patients are referred from places more than 50 miles away, and in such cases little can be done besides making a diagnosis, unless patients are admitted, which is undesirable for more than a very few. The answer is not to set up such clinics everywhere, because (Dr Lawson estimates) a catchment area with a population of 2 million is needed to provide the 50 new cases a year that the staff must see to get enough experience. Such clinics should probably be at hospitals, because for complete diagnosis audiometry, electroencephalography, and other aids are sometimes wanted. There is a need for perhaps one or two diagnostic clinics in each great city or conurbation, but (apart from exceptional cases) they need treat only the children who live on their doorstep. Most of the rest could probably be treated adequately in the various kinds of institution specified by Dr Ellis, with guidance by the special diagnostic centres, which could serve both as examples of the best in treatment and as places where new methods are explored. And in our concern for children, we must not forget the needs of the increasing numbers who survive to adult life with cerebral palsy. On p. 842 Dr Palmer reminds us of their special problems and shows what can be achieved.

Finally, Professor Moncrieff wonders whether a child with cerebral palsy should ever go to a normal school. Among the often neglected disabilities to which he draws attention, besides deafness and sensory defect, is the emotional warping. He quotes R. K. Byers, of Boston, as saying that the yardstick of successful treatment now is not motor development but emotional adjustment. The child with cerebral palsy is not a source of joy to his parents, and is surrounded by anxiety. More interest than hitherto should be given to supplying emotional and sensory experience, instead of concentrating only on motor defects. The child with cerebral palsy differs much from a child of the same intellect and motor disability who lived a normal life for a few years before having, say, poliomyelitis, and the same type of school may not be suitable for both. "It is something to be worked out." A spastic child may be distracted, bewildered, and upset among normal children, and may even make better progress in isolation.

It is clear that, on many topics, those who have done most work on cerebral palsy are not in agreement. We need more exact knowledge of the results of various methods of management, and investigations into the causes and prevention of cerebral palsy, not so much now by retrospective inquiry as by prospective and physiological investigations. The therapeutic work is as important as it is valiant, and will long be needed, but there is a limit to what even the most devoted and skilful therapist can do, and we must find ways of preventing the disability more often. The two national societies have done a valuable service in calling attention to cerebral palsy, stimulating research, and coordinating activity. So far as the medical profession is concerned, this is being continued by the National Spastics Society's issue of a new quarterly journal, the *Cerebral Palsy Bulletin*,[29] edited by Dr E. Clayton-Jones, which hopes to "stimulate interest in the scientific and clinical aspects of the various forms of cerebral palsy." This issue contains a brief biography of Little (which recalls that his first account of "Little's disease" appeared in this journal[30]) and a reprint of his paper read to the Obstetrical Society of London in 1861, based on 200 cases he had seen. The next issue will contain abstracts from and comments on recent publications.

The two national societies may be relied on to go on with their excellent work, but we must agree with Professor Moncrieff that it is not in the best interests of the patients (or of those whose admirable voluntary efforts are duplicated) that there should be two societies, and we hope that means can be found for their fusion.

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[27] Collis, E. *Lancet*, 1953, ii, 757.

[28] Collis, E. *ibid.* 1953, i, 416.

[29] *Cerebral Palsy Bulletin* 1958, no. 1. Published for the medical advisory committee of the National Spastics Society, 28, Fitzroy Square, London W.1. Pp. 36. 2s. 6d.

[30] Little, W. J. *Lancet*, 1843-44, i, 318, 350.

Annotations

USE AND TOXICITY OF SULPHONAMIDES

SULPHONAMIDES have been in use for over twenty years Starting with the original 'Prontosil Rubrum', the aim has been to find derivatives which are more potent in antibacterial activity and less toxic to man It is an advantage if the frequency of administration can be reduced, so that disturbance of the patient at night can be avoided without the blood-level falling below that required for therapeutic effect The sulphonamides now in common use, either singly or in various mixtures, for the treatment of systemic infections include sulphathiazole, sulphadiazine, sulphamerazine, and sulphadimidine

It is doubtful whether, as regards antibacterial activity, there is much difference between these four compounds The choice should accordingly be based on toxicity, absorption, persistence of effective concentration in the blood, and frequency and convenience of administration In these respects the four differ considerably Sulphathiazole is undoubtedly the most toxic, being especially liable to cause rashes and drug fever It and its acetyl derivative are relatively insoluble in acid urine, it is rapidly excreted, and frequent administration is required to maintain an adequate blood concentration Sulphathiazole appears in the *British National Formulary, 1957* but is omitted from the *British Pharmacopœia, 1958* Sulphadiazine and sulphamerazine are less liable to cause generalised toxic effects, but they and their acetyl derivatives are relatively insoluble in urine Dr Arneil, in his article this week, draws attention again to the particular danger of sulphamerazine causing hæmaturia in children Sulphadimidine is safer since it is relatively soluble, even in an acid urine, in both its free and acetylated form [1]

The risk of injuring the kidneys with sulphathiazole, sulphadiazine, and sulphamerazine may be reduced by ensuring a high fluid intake to increase the volume of urine and by making the urine alkaline Unfortunately, these precautions are troublesome and sometimes neglected, and often insufficient alkali is given Recognising these difficulties, Lehr [2] introduced the principle of sulphonamide mixtures to reduce the liability to crystal formation in the urine The tendency to crystal deposition varies with the concentration of each individual sulphonamide, and thus is considerably less in a mixture of several compounds, but the therapeutic effect is that of the total concentration The *National Formulary* describes trisulphonamide tablets for adults and a mixture for infants containing sulphathiazole, sulphadiazine, and sulphamerazine

The question arises whether there is still any place for these more toxic sulphonamides, even in mixtures, for many antibiotics, on the whole less dangerous than the sulphonamides, have been introduced—including phenoxymethylpenicillin, which can be given by mouth There is probably no sufficient reason for retaining the relatively toxic sulphathiazole in sulphonamide mixtures [2] The closely related compounds—sulphadiazine, sulphamerazine, and sulphadimidine—differ little from sulphathiazole in their absorption, their penetration into the cerebrospinal fluid, and the ease with which a therapeutic blood-level is maintained Sulphadimidine shows slightly greater plasma binding and conjugation than the other two compounds,[3] but it is doubtful whether this substantially affects therapeutic efficacy Sulphadimidine is much less likely to cause renal damage, and is therefore preferable certainly to any single component of the official mixtures and probably to the mixtures themselves The practising doctor may be well advised to avoid entirely the more hazardous preparations—sulphathiazole, sulphadiazine, and sulphamerazine—either singly or in combination with each other or with antibiotics This applies especially to sulphamerazine for children, in whom the risk of hæmaturia is particularly great If administration of sulphadimidine is not followed by adequate response, a change should be made to a suitable antibiotic and not to another sulphonamide or a mixture of sulphonamides On the other hand sulphadimidine (and possibly newer equally non-toxic sulphonamides which have not been so fully evaluated) still have a definite place in therapeutics They are especially valuable in meningococcal septicæmia and meningitis, and in certain urinary-tract infections But the use of even these sulphonamides is not without risk, and attention must always be paid to dosage, renal function, and fluid intake

THIRST

THIRST—the uneasy or painful sensation caused by want of drink, as the Oxford Dictionary defines it—being subjective is difficult to investigate But if it can be assumed that in laboratory animals drinking implies a state analogous to thirst, then a dry mouth is not the whole story [4] and a "drinking-centre" exists Pure water-deficiency results in thirst, but hyperosmolarity is unlikely to play a large part because the hyperosmolarity associated with other disturbances—for example, increased blood-urea—does not increase thirst unless there is an accompanying diuresis A change in the distribution of body-fluid may be important Thus, salt depletion can give rise to a sensation of thirst that is not slaked by pure water but can be relieved by small amounts of hypertonic saline solution [5] Salt depletion causes the extracellular-fluid volume to contract, and it seems that shrinkage of this volume results in the urge to drink Removal of a large volume of extracellular fluid, such as isotonic ascitic fluid, also leads to thirst the paracentesis cannot affect the osmotic pressure of the body-fluid, but it does affect its total volume and compartmental distribution Thirst has been noted [6] as a symptom of impending diarrhœa, because, it is believed, of the reduction of volume of extracellular fluid following sequestration of isotonic fluid in the lumen of the intestine It seems, therefore, that although a rise in the osmotic pressure of the body-fluids without change in volume *may* lead to thirst, changes of the volumes in fluid compartments *always* lead to thirst

Most of the work on the neural integration of thirst has been done in goats Polydipsia results from hypothalamic stimulation, either by local injection of 2% sodium chloride or by electrical stimulation [7] Direct evidence of a "drinking-centre" in man is difficult to obtain, though rare cases are described in which diabetes insipidus and anterior-pituitary insufficiency together allow a greater loss than intake of fluid, leading to hyperosmolarity of body-fluids The effect of impulses from peripheral nerves is evident in the influence on the drinking response of a dry mouth and of gastric distension with a balloon,[8] and in the pharyngeal "metering" of fluid intake in dogs with œsophageal fistula[9] The evidence so far has led to the postulate[10] that the hypothalamus contains receptors which regulate water intake as well as output, and presumably receptors concerned with intake are stimulated, partly by changes in the volume of the fluid compartments, and partly by afferent impulses from the gastrointestinal tract.

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CERVICOTHORACIC GANGLIONECTOMY

THE results of cervicothoracic ganglionectomy in the treatment of arterial lesions reflect the selection of patients submitted to operation rather than the particular technique of sympathetic interruption Raynaud's disease as defined by Allen and Brown[11] must have been present bilaterally for at least two years, the colour changes occur on exposure to emotion or cold, and gangrene or any primary associated disease such as acrosclerosis are absent Gifford et al[12] review 70 such patients, all women and mostly below 40 years of age, who some years ago were submitted to resection of the stellate ganglion, and often the second thoracic Their results mirror those already published less than half the patients definitely benefited, and in some the disability was actually enhanced Gifford et al agree that the results in secondary Raynaud's phenomenon, such as may accompany acrosclerosis, are the worst, while those in the lower limb are better than those in the upper limb Their data do not reveal any way by which the results of sympathectomy in the upper extremities can be predicted in advance, except that good results were obtained more often when complications of Raynaud's disease, such as nutritional changes, were not present before operation Before deciding to operate it is important to exclude the many other conditions which may be associated with digital colour changes—particularly the so-called collagen diseases Most patients with these other disorders are in no way helped by sympathectomy, and in some the primary disease may be aggravated Raynaud's phenomenon due to a local fault, such as sometimes follows prolonged use of a vibratory tool, is not benefited; but where the sympathetic impulses play an essential part in the causation of symptoms interruption of the nervous control will be followed by great relief What is much needed now is a simple clinical test to establish the relative importance of the various factors which contribute to the Raynaud phenomenon

IMMUNOLOGY

IN view of the importance of immunological phenomena in medical and veterinary practice as well as in the wider fields of biology, it is surprising that hitherto Britain has had no scientific society devoted mainly to advancing our knowledge of immunity In many countries—notably the U S.A and Germany—active immunological societies with specialised journals of international repute have existed for many years In recent years the scope of immunology has increased enormously, and it now encompasses the increasingly important subjects of allergy, auto-antibodies and their possible role in the pathogenesis of many common diseases, and homograft immunity and acquired tolerance In addition, it has a large stake in genetics, mainly by virtue of its importance in the realm of blood-groups and blood-group substances, as well as lesser but none the less important interests in the pathogenesis of tumours On a slightly less biological level it claims many devotees in the fields of pure chemistry and physics This growth pressure led to the formation, in the autumn of 1956, of the British Society for Immunology The necessity for a journal of its own was immediately appreciated by the new society, and within fourteen months of the inaugural meeting there has appeared the first issue of *Immunology*,[1] the society's official journal, under the editorship of Prof J R Marrack.

This issue confirms the greatly widened range of the subject Thus the opening paper, by P B Medawar and P S Russell, on adrenal homografts in mice with special reference to immunological adrenalectomy, deals with how to overcome the immune reaction that at present vitiates the most skilful attempts to transplant tissues from one individual to another The paper by B Cruickshank and A. R Currie on the localisation of tissue antigens by the fluorescent antibody technique is a further example of the extension of this exciting immunological method[2] into other fields of physiology and pathology Other contributors show well the present physical trend in immunology, and the more chemical approach is represented by a study of the components of mycobacteria that influence antibody production

A CHAIR OF PÆDIATRIC SURGERY

THE news of the appointment of Mr A W Wilkinson as the first professor of pædiatric surgery at the Institute of Child Health in the University of London (see p 861) is of exceptional interest, for there is only one similar chair in the world—at Boston, Massachusetts It is fitting that such a chair should be established at the Institute, for the associated Hospital for Sick Children, Great Ormond Street, has been the scene of pioneer work on surgery in the young, which the new academic unit will be able to consolidate This development has been made possible by a gift of £80,000 from the Nuffield Foundation, to mark Lord Nuffield's 80th birthday It was at the Institute that in 1945 the first Nuffield chair—that of child health—was created

THE BUDGET

IN the past year the level of unemployment has risen from 1 7% to 2 0% Mr Heathcoat Amory, the Chancellor of the Exchequer, when he introduced his first Budget last Tuesday, would no doubt have liked to stimulate demand by sweeping cuts in taxation But Britain's falling share of world trade, and the continuing need to strengthen sterling, prevented such a move, and his main tax concession consists in curtailing the rate of purchase-tax on goods subject to this tax at the highest rates The limits of income-tax exemption for the elderly are to be slightly raised, and the aged relief limit is to go up from £700 to £800 These concessions, though they are not large and affect only some of the elderly, give welcome recognition to the difficulties of this section of the population in making ends meet

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Special Articles

A CEREBRAL-PALSY SERVICE FOR CHILDREN

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THE cerebral-palsy unit at Queen Mary's Hospital for Children, Carshalton, has been running continuously since 1943, and the parental-advice clinic since 1945. In August, 1957, 157 patients were in the care of this service: 17 were in the residential unit and 140 were attending the advice clinics with their parents. Of these 140, 59 had attended for up to three years, 47 for from three to six years, 27 for from six to nine years, 6 for from nine to twelve years, and 1 for thirteen years.

This article analyses the experience of the diagnostic clinic and of the new entrants to the advice-clinic service over the years 1954–56, during which time 206 cases were referred.

The principles underlying the running of this unit have been described by Collis et al. (1956), and only the structure of the service will be outlined here.

There is an inpatient unit of 20 beds, within a general children's hospital, working in close cooperation with a hospital school, and including on its staff two specially trained teachers.

New patients are seen with their parents at a diagnostic clinic where, following history-taking and examination, a decision is taken on the following questions:

1. Is this a case of cerebral palsy?
2. If it is, what type is it, and to what extent, if at all, is there evidence of a complicating mental defect?
3. Are there already incipient or established secondary deformities?

In difficult cases a decision may be delayed until after a period of observation in the inpatient unit.

The prognosis, both physical and mental, is then explained to and discussed with the parents, and the services of the advice clinic are offered to them.

They are told that the day-to-day management and guidance of their children does not need any special technical facility, and that affected children will make better and faster progress if they are looked after by their parents. The day-to-day continuity of treatment needed is such that nobody but the parent can carry it out, unless the child is to be admitted for a very long period to a heavily staffed unit, and thus separated from his home for long periods during his formative years. When parents accept this offer, advice-clinic visits are arranged at about monthly, and later at longer, intervals.

The limited purpose of what follows is to analyse the initial assessment of cases and the extent to which advice-clinic services are accepted and used, and to point to certain unresolved problems which may be of wider interest.

ANALYSIS OF CASES

Of the 206 patients referred to the clinic in 1954–56, 68 were found to have mental defect only, and the parents were given advice by the almoner or referred to the mental health authorities where appropriate. 11 children were found to have neither cerebral palsy nor mental deficiency. Most of these were normal children whose progress, though it had given cause for alarm, was considered to be within the normal range. The remaining 127 had cerebral palsy in one of its forms, with or without some mental defect. These cases fell into the following clinical categories:

Generalised spasticity	76 cases
Variable rigidity	19 cases
Athetoid cerebral palsy	3 cases
Ataxia	3 cases
Congenital hemiplegia	21 cases
Acquired hemiplegia	5 cases

Of these 127, 38 did not initially accept the services of the advice clinic for various reasons, among which geographical reasons predominated. The remaining 89 accepted the service offered, but of these 28 had ceased to attend within a few months. The reasons for this cessation were again largely geographical, but some who stopped had accepted other advice, and in some the cerebral palsy was complicated by such severe mental deficiency that institutional management elsewhere was arranged at parental request. Of the original 127 cases, therefore, only 61 (48%) effectively accepted the advice-clinic services.

This clinic acts to some extent as a reference clinic for cases over a wide area, and for those who come a long distance it is often impossible to offer more than diagnosis and initial advice. Of the 127 cases, about 40% came from the London or Surrey areas, 20% from other counties near London, and 40% from more than 50 miles away.

The services of the advice clinic are invariably offered to all who wish to come, whatever the degree of mental defect, but it is the parents of the most severely mentally affected children who most commonly fail to make consistent use of the service, because it is to them that it has least to offer.

Intelligence

Following clinical assessment, the cases are grouped into one of four intelligence levels, in terms of the probably appropriate form of education or training at school age:

1	Probably capable of receiving education at a normal school	31 (24%)
2	Requiring education in an educationally subnormal school	30 (21%)
3	Borderline of educability	18 (14%)
4	Ineducable	48 (38%)

The probable social prognoses, taking account of both mental and physical disability, were as follows:

Independent	36 (28%)
Partially dependent (that is to say, probably capable in due course of taking up limited and carefully arranged employment, but not capable of living a fully independent life)	26 (20%)
Dependent	65 (51%)

Ætiology

It is seldom possible to assign a cause with certainty in individual cases. For example, though there is a definite association between cerebral palsy and fœtal or neonatal anoxia, the extent of this anoxia is not measurable, and many infants suffer anoxia without developing cerebral palsy. The analysis of a large series, however, may well show significant associations. Among the various factors analysed in the case-histories, the following were found:

Definite clinical evidence of neonatal anoxia	40 cases (31%)
Maternal toxæmia	10 cases (8%)
Long or difficult labour	17 cases (13%)
Long-continued neonatal jaundice, including hæmolytic disease of the newborn	16 cases (13%)

Many cases of cerebral palsy could be diagnosed earlier than at present if all babies with a history of any maternal disease or complication of pregnancy, labour, or the neonatal period were followed up carefully for a year or two Even if this were done, however, a substantial proportion of cases would still be found to arise in babies without such histories Of the 121 cases of congenital cerebral palsy in our series, in 43 (36%) there was no history of any of the following antepartum hæmorrhage, anoxia, forceps delivery, maternal toxæmia, precipitate labour, long or difficult labour, long-continued neonatal jaundice, hæmolytic disease of the newborn, birth-weight under 3 pounds It is difficult to see how these cases could be picked up at the earliest opportunity, except by a careful follow-up of all babies In view of the very large numbers of babies concerned this could probably be done on a national scale only by the reference from baby clinics of all babies showing evidence of delay or abnormality of motor development. (In the case of the 68 children found to have mental defect only, 37 (55%) had no such history of abnormality)

Birthweight

Of the 109 cases in which reliable birthweights were obtained, 6 were over 9 lb , 53 between $5^1/_2$ and 9 lb , and 50 under $5^1/_2$ lb The incidence of prematurity was therefore 45%

Age at Referral

One of the most serious practical problems arises from the late age at which children are referred to the diagnostic clinic. It is extremely important that the diagnosis should be made early, so that the baby may be appropriately handled and guided in the acquisition of motor patterns, thus making the best use of his limited capacity from the start, and avoiding so far as possible secondary disorders of function and structure. Of the 127 children, only 13 (10%) were referred in the first eighteen months of life, a further 41 (32%) between the ages of 18 months and 3 years, 29 (23%) between the ages of 3 and 4 years, and 44 (34%) over the age of 5 years

Mental Defect With and Without Cerebral Palsy

To satisfy the parents of a mentally defective child that the child's life is not further complicated by a motor deficiency is a substantial and valuable part of the clinic's work. This opinion we have been able to give in 68 of the 206 cases referred to us The cases of mental defect or cerebral palsy or both constitute between them 195 of the total number of 206 cases referred to us These 195 cases have been classified to show the number of cases from each source and the proportion of these which were found to have mental defect only

Source	*No referred*	*Proportion found to have mental defect only*
Hospital service	76	24%
Local-authority medical officer	25	36%
General practitioner	42	40%
Parents	38	45%
Lay society	13	46%

ADMISSION TO RESIDENTIAL UNIT

Of the 86 patients who initially entered the service, 22 were admitted to the unit either for extended diagnosis or to get management firmly started along the right lines both for the mother and child, and a further 18 were subsequently admitted either because the child had difficulties in getting management effectively started as an out-patient, or to help the mother over a socially difficult period Of these 86 cases, therefore, a total of 40 (just over 45%) spent some time in the residential unit itself This was not a substitute for the system of parental care and guidance, but a necessary entree to it

DISCUSSION

Prompt Diagnosis

This can probably best be secured by the reference to experienced diagnostic clinics of all infants in whom there is any suspicion of abnormality or delay in motor development

Early Management

Early diagnosis is not always followed by immediate measures of management. Commonly when cerebral palsy has been correctly diagnosed in the 1st year of life the parents are told that nothing can be done until the child is 3 or 5 years of age By this time, failure to provide day-by-day guidance of the child's developing physical activity has resulted in avoidable abnormalities of function and of structure

Geographical Factors

Although this clinic operates in a fairly dense urban community, in close proximity to nearly 10 million people, 40% of the cases are referred from over 50 miles away, from which distance it is almost impossible to maintain the close contact which is needed if anything beyond diagnosis is to be offered Nevertheless it is difficult to see how the staff of a cerebral-palsy unit can acquire facility in the diagnosis and management of these cases without a diagnostic turnover of about 50 cases a year This turnover would correspond to the exclusive intake from a population of about 2 million (Collis et al. 1956)

Education

Experience shows that if the child is appropriately handled from the earliest years, so that by the time school age is reached he has at least three years of effective management behind him, he will be able to fit into the pattern of normal and special educational services provided or envisaged under the 1944 Education Act, and that the type of provision required will be decided more by his intellectual capacity than by his residual physical disability

It is vital that there should be close cooperation between doctor, teacher, and parent, but this we find difficult to achieve if the parent has not several years of guided experience behind her before school starts, and if the children attending an advice clinic are scattered among many schools The latter difficulty has led to the suggestion that special schools for cerebral-palsied children as such should be provided This view overlooks the very wide scatter of intelligence level in these children, which varies between the highest and lowest intelligences for which the education authority is responsible, but with a strong bias towards the lower levels A school for all cerebral-palsied children in the locality would, therefore, despite its small size, have to cater for a wider variation in intelligence levels than is provided for either in normal or in educationally subnormal schools

A compromise solution might be possible at least in densely populated areas The cerebral-palsied children could be educated in the type of school (normal, educationally subnormal, or physically handicapped) which would best suit them, but over a wide area they could be concentrated so far as possible in selected schools of the appropriate type, working in close conjunction with a cerebral-palsy advice service Even under these conditions great care would have to be taken that each child's education was planned according to his individual requirements rather than his verbal diagnosis This applies especially to the more gifted children, who, because of their higher intelligence and greater learning ability, will overcome their physical disability more rapidly and more completely than others and may well be able to do without any special educational provision

SUMMARY

In 1954–56, 206 cases were referred to the cerebral-palsy diagnostic and advisory service

34% of these patients were found to have mental defect only The exclusion of cerebral palsy in mentally defective children has become almost as important a part of the diagnostic-clinic service as the diagnosis of cerebral palsy itself

Of the children with cerebral palsy, about a quarter were regarded as sufficiently intelligent to receive normal education, while nearly 40% were probably ineducable

It is estimated that nearly a third should eventually be capable of leading a completely independent life in society, while *just over half will always be fully dependent*

40% of cases were referred from distances of over 50 miles The services of the advice clinics were offered in all cases of cerebral palsy, and were accepted in just over half the cases

Only 10% were referred in the first 18 months of life, and 34% were already of school age at referral

The figures confirm the ætiological importance of certain disorders or complications of pregnancy, labour, and the neonatal period in the ætiology of cerebral palsy, but in 36% of cases no such history was obtained In 45% of cases birth was premature (under $5^1/_2$ lb birthweight)

While accepting sole responsibility for the views expressed here, I wish to record a deep debt of gratitude to Mrs Eirene Collis, who has been continuously in day-to-day charge of the cerebral-palsy unit since she started it in 1943, and on the basis of whose devoted work my experience of cerebral palsy has been gained in a close cooperation over the past four years

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PRESTED HALL

A RESIDENTIAL CENTRE FOR ADULT SPASTICS

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Prested Hall is a residential centre for thirty men and women severely handicapped by infantile cerebral palsy It was opened by the National Spastics Society in January, 1955, and is leased to the society for a token rent The treatment unit was built by the society in the spacious grounds attached to the Hall This is, I believe, the only centre in the world catering for adult spastics offering residential physiotherapy, occupational therapy, and speech therapy, with an opportunity to lead a fuller life than is normally possible for a handicapped person in a home or institution

PROBLEM

Almost all the residents at Prested Hall are adults who have had no specific treatment for their condition and little or no special education In 3 years, ten were admitted mainly because their parents, owing to age and infirmity, were unable to care for them One came from a mental hospital where he had spent 30 years Twenty-five were admitted specifically for physical treatment and training The remaining eight were admitted from geriatric and chronic-sick units, where their companions were often more than twice their age With improvements in the care of young spastics, and more understanding of their problems and their possibilities, the proportion of admissions in the third group should decrease At present many of the admissions to any adult centre must be patients who have had no previous purposeful care and have been for years virtually relegated to the scrap-heap

The spastic presents an inextricable mixture of social, emotional, and physical difficulties Most of those who have been cared for at home have been grossly overprotected and have never been encouraged to do even simple things for themselves Some have been dressed and undressed daily by their mothers up to the age of 30 or 40 One was kept indoors for the greater part of her life, though quite capable of using a self-propelled wheel chair Such patients have learnt to depend on others and do not take easily to attempts to make them *work towards their own improvement* Some are frustrated because their disability restricts them, some have been robbed even of the wish to do things and are beyond frustration

For most, the first months at Prested Hall are their first attempt at living on equal terms with other people The new adjustment is not easy Initial reactions run the whole gamut from morbid shyness to aggressiveness In the first months after the centre was opened, this led to very considerable difficulties, but as time has passed a nucleus has developed of well-adjusted residents whose stability is a material aid to newcomers

On the physical side, *difficulty in locomotion* is probably the biggest problem The previously untreated patient has had to make some use of his arms and hands, but has not usually been encouraged to move about He is afraid of falling and is often handicapped by defective kinæsthetic sense in his legs and sense of balance A good deal of incentive and encouragement is needed to make him feel that the effort and concentration demanded by learning to walk is really worth while

DOCUMENTATION

Records are kept of all residents They include a family history where available, but, as one might expect with adults the history of confinement and early childhood was often unobtainable Capability charts are kept of daily living activities These are as simple as possible complicated graphs have been found impracticable and unnecessary Still photographs are taken of every resident in standard positions and are repeated yearly or after a major change in ability Ciné photographs are also taken of each resident performing standard tasks, including eating, drinking, and moving by whatever means possible The object is to record maximum capability, to study movement pattern, and to teach and encourage the patient The classification of the cases seems more difficult as more experience is obtained It appears possible to divide them only into predominantly spastic, athetoid, or ataxic types In almost all cases they are mixed Even in apparent hemiplegia, some defects are usually found on the opposite side There is also a proportion of additional abnormalities, including four cases of congenital deformity of the hip, one of spina bifida occulta, one of epilepsy, five of partial deafness, two with marked nystagmus, and four with marked short sight

CAPABILITY CHART ASSESSMENT IN A CASE OF DOUBLE SPASTIC HEMIPLEGIA

				brought forward	46		*brought forward*	96		*brought forward*	141
1	Dressing	3	16	Sitting in bath	4	31	Sit on normal chair	4	46	Position sense	4
2	Undressing	3	17	Washing in bath	4	32	Walk alone 100 yards	0	47	Shape and texture	3
3	Buttons	3	18	Brushing hair	4	33	With callipers	5	48	Make a bed	3
4	Shoes or boots	4	19	Combing hair	4	34	With sticks	3	49	Replace sheets	2
5	Laces	3	20	Continence	5	35	With crutches	5	50	Turn mattress	1
6	Tying a bow	3	21	Sit on W.C. seat	4	36	Walking machine	5	51	Thread needle	3
7	Callipers on and off	5	22	Use paper	4	37	Assisted by one person	5	52	Use needle	3
8	Washing	4	23	Flush	5	38	Crawling 5 yards	5	53	Clean shoes	3
9	Clean and cut fingernails	4	24	Blow nose	4	39	Up and down stairs	3	54	Wash shirt or blouse	3
10	Clean and cut toenails	3	25	Drink from cup	0	40	Self-propelled chair	5	55	Wringing	3
11	Cleaning teeth	4	26	Drink from mug	4	41	Tricycle	1	56	Pressing	3
12	Gargle	0	27	Drink with straw	5	42	Talk	4	57	Make a cup of tea	3
13	Shaving hair-slide	3	28	Use a spoon	3	43	Read	0	58	Cut bread and butter	0
14	Getting in bath	2	29	Use spoon and fork	0	44	Write with pencil	0	59	Cook egg and bacon	0
15	Getting out of bath	2	30	Use knife and fork	0	45	Type	0	60	Prepare lunch	0
	carried forward	46		*carried forward*	96		*carried forward*	141		*Total*	175 (58%)

Code 5, normal 4, reasonably well 3, well but very slow 2, not well, needs assistance 1, attempted 0, unable Maximum 300

METHOD

The centre is run with very few rules, and provides conditions as near to home as is possible with a community of this type. It has the advantage that the residents realise that there are other people with similar disabilities which they are striving to overcome. They improve with competition and an incentive is provided which they do not have at home.

The accommodation is divided into two-bedded and four-bedded rooms. Those with the most severe handicaps, dependent on wheel chairs, live on the ground floor. Washing and toilet facilities have been arranged for handicapped persons and include a wooden wheel chair for use with the shower. The cost is £12 a week for each resident. Most of this is met by the appropriate welfare authority. The National Assistance Board now contributes 40*s.* a week and 10*s.* a week pocket-money.

TREATMENT

Treatment in the *physiotherapy* department aims at increasing the resident's ability to perform everyday activities, including dressing and washing, progressing where possible to complete independence. The methods followed at first were compiled from the normal sequences of development on the lines on which most children are treated. This did not work well with adults, who have well-established movements, usually in a bad pattern. The method now used is to facilitate the righting and protective reflexes and balancing reactions, and to treat contractures and scoliosis. One handicap common to almost all adult spastics is the malformation of their feet. This may be lessened by well-fitting surgical boots and shoes.

The aim of treatment in the *occupational-therapy* department is to develop any latent skills, to assess ability to work through various tasks and crafts, and, as in the physiotherapy department, to create as great a degree of independence as possible. The patient must be treated as a whole. It is not only the ability to do a particular task but a willingness to do it and sufficient concentration to work for an economic period. Residents are encouraged to take part in group activities such as debating, play-reading, and puppetry. A kitchen unit, provided by a local Women's Institute helps to fulfil a desire to partake in normal household activities, which have often been denied at home. It has proved one of the most successful ways of preparing residents for future independence. It was thought that many aids and appliances would be needed in the kitchen to suit the residents' disabilities. This proved to be wrong. A work-bench, oven, and sink were provided at a height suitable for a wheel chair. A pull-out table, containing holes for mixing-basins, and two hand-grips were all the aids needed. The residents solved their own problems and it was found better to encourage them to overcome their disabilities without gadgets. There was a great need for elementary education, and lessons were started in the occupational therapy department. These lessons are now being continued as a night class through the local education authorities, aided by one of the residents who has passed three subjects of his general certificate of education.

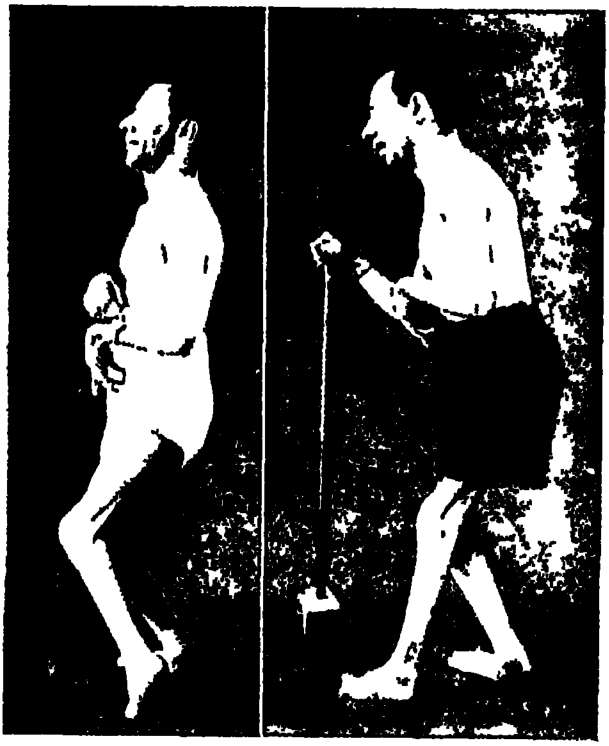
The principles which have been followed for *speech therapy* have been based on the following: general relaxation and positioning of the patient, exercises to improve control and depth of breathing, lip exercises to improve lip muscles, manipulation of the tongue, lips, and jaw to increase range of movement, stimulation of palatal movement, and mirror training to coordinate sound and movement by imitation, and to gain control of facial expression.

Eighteen patients out of thirty receive speech therapy. Only four of these can turn up the tip of the tongue on protrusion, thus sounds usually produced with the tip of the tongue on the alveolar ridge (e.g., t, d, l, n) are imperfectly formed. Inability to move the tongue to the side, occasionally only one side, is another difficulty. The tongue is often underdeveloped, and moving the middle of the tongue backwards, as in eating, is defective. Eating and drinking movements are therefore taught in the same department. In one case a dental gag has been made by a local dental surgeon for a resident who is unable to close his lips. This gag contains a 'Polythene' tube and enables him to close his mouth and suck fluids. Before he can close his mouth round this he has to stimulate his lips by stroking them. It is hoped to reduce gradually the size of the gag and finally discard it. Dribbling is fairly common. It has been improved in several cases by encouraging the patient to exercise more conscious control of the swallowing reflex.

An imperfect speech pattern may be the easiest for the spastic to acquire, but where it has failed to convey the patient's thoughts it has caused frustration. In many cases correct guidance during childhood would have produced far better speech and may well have led to better understanding.

Surgery.—Only one resident has been operated on—for flexion contractures affecting his knees.

He was 31, and before operation walked on his toes with his knees bent to about 135° (see figure, a). These knees could not be straightened under anæsthetic. After operation his knees were straight and he could place both feet flat on the ground (b). It took 8 months of daily treatment before



(*a*) (*b*)

Operation for flexion contracture of knees (*a*) before, (*b*) after

he could walk as well as before the operation. This was nearly 2 years ago, and he is now more stable than before and walking better. The delay, which might well have led to failure, was probably caused by a number of factors. The patient's pattern of walking was well established. With his feet flat on the floor there was a major change in this pattern which was very difficult for him to appreciate. This operation included a tendon release, which deprived him of part of his muscle and tendon sense, changing his reflex pattern. His drive and endurance was overestimated.

No doubt there is a place for surgery in the adult spastic, but the advantages must be very carefully considered beforehand, and endless time and patience may be needed in the after-treatment.

RECREATION

Before their arrival the residents had had almost no experience of playing games. Their reaction to ball games was that they could not and did not want to play. This attitude changed very quickly and they now enjoy modified games of tug-of-war, cricket, croquet, and football, and take part in obstacle races. The team spirit is encouraged and teams are so picked as to balance their handicaps as evenly as possible. As a result of this, big movements, involving hand and eye coordination and balance, have improved noticeably.

The residents are encouraged to manage their own affairs through their own social committee. Entertainment for those who wish to take part is provided in the lounge in the evening, and there are frequent social outings to the theatre and places of interest.

CONCLUSIONS

The treatment and management of adult spastics was approached with caution, and no dramatic results were expected. In the course of 3 years' experience the results have been encouraging. Only two out of eleven women residents could walk when they first came to Prested Hall. At the end of the first 8 months nine could walk on their own or with some mechanical aid. Of the men nine out of eighteen could walk, with or without aids, and this number was increased to eleven in the same period.

Given a chance to follow an occupation and to learn a remunerative trade, most residents have shown an ability to improve their dexterity. Two have achieved independence in a sheltered workshop. Four have improved enough to pass on to another of the society's centres for more advanced training. Five were discharged as unlikely to improve with further treatment. Two left because their local authorities withdrew their grants. One died as a result of an epileptic fit.

In seeking employment, one of the most difficult obstacles is the average employer's reluctance to take on a spastic—not necessarily because of his physical limitations, but because of his appearance. This should improve as the condition is more widely understood by the lay public. Another difficulty is the trade-union rate for the job. Most spastics are unable to work economically because they are slow, but they are quite capable of doing a good job, if they can be paid what they are worth and if they do not hold up a production team. The spastic's appearance suggests that he is accident-prone, but though there are two electric lathes, an electric drill, many sharp tools in the occupational-therapy department, and the usual kitchen ware in the kitchen, there have been no accidents so far. This suggests that spastics are not as clumsy as they often appear.

FUTURE

There is undoubtedly a need for assessment and early training of spastics before admission to industry or a specific training-centre. Unfortunately there will always be those who cannot live independently or even work economically in sheltered conditions. It will be possible to make these less dependent and more able to appreciate a fuller life by a stay at such a centre, even if they eventually have to return to their homes or some type of institution. For the future we must look to the children, and if possible prevent or reduce the incidence of spastic disease, for there is no cure. With a better understanding and better treatment of spastic children, we should see less deformity, both mental and physical. When a child is found to be spastic, the aim must be maximum capability, making the most of the remaining undamaged part of the brain.

I am grateful to Dr J D Kershaw, a member of the centre's committee, for his advice on this paper, to Mr J H Watson, the warden, and to members of the staff whose cooperation and team work have made this treatment centre possible.

AN ORAL CONTRACEPTIVE

ON April 9, at the London School of Hygiene and Tropical Medicine, Dr GREGORY PINCUS gave the second Oliver Bird lecture, on Fertility Control with Oral Medication. Sir Russell Brain, president of the Family Planning Association, took the chair.

Experiments five or six years ago, said Dr Pincus, showed that though the normal function of progesterone was to help pregnancy by ensuring implantation of the ovum, in large and appropriately timed doses it would inhibit ovulation in all species and prevent fertilisation. Since injections of progesterone were painful, and oral doses not very effective, allied compounds were sought in the hope of finding one that would be more effective by mouth. Three 19-norsteroids emerged, all especially active in inhibiting ovulation. 'Norlutin,' 'Enovid,' and 'Nilevar'—or compounds I, II, and III respectively Of these enovid was the most potent inhibitor of fertility in the rat and of ovulation in the rabbit It had some progestational effect, but less than progesterone, and some œstrogenic effect

The three compounds were tested for their effect in inhibiting ovulation in women—first in volunteers, giving one 10 mg tablet daily from the 5th to 24th days of the menstrual cycle, then in patients in a mental hospital The indices of ovulation used were (1) the peak of temperature, (2) vaginal smears, (3) endometrial biopsy, and (4) urine output of pregnanediol In the volunteers, with compound I, the mean length of the menstrual cycle was unchanged, evidence for ovulation was lacking in 76% of cycles by endometrial biopsy and in 92% by other tests, and pregnanediol excretion fell to a tenth of normal At laparotomy in 12 women, no evidence was found of recent ovulation When treatment was stopped, normal cycles were resumed, though the first was delayed The findings with compounds II and III were similar In the mental-hospital patients, there was some shortening of the cycle with compound I, but not II The plasma-free corticoids were increased or unchanged, and the plasma-bound corticoids decreased With compound II, there was diminished excretion of corticosteroids, pregnanediol, and gonadotrophin

A field trial was then begun, in cooperation with the Family Planning Association of Puerto Rico, to test the contraceptive effects of enovid Women were given tablets and told to take one daily from the 5th to the 24th day of the cycle, and were visited monthly by social workers who asked them how many tablets they had in fact taken, if they had missed any they were advised to go on till they had taken all twenty 70% of the women took the tablets daily as prescribed, in these the cycle length was normal, with a less wide range of lengths than is found in untreated women, in those who missed one to five tablets the cycle tended to be shorter or longer than normal, and in those who missed more than five the cycle tended to be longer The output of corticosteroids in the urine was decreased, the hæmoglobin and clotting-time remained the same, and the bleeding-time became a little shorter The menstrual flow seemed unchanged but there was a tendency for dysmenorrhœa to be relieved Endometrial biopsies revealed much the same picture throughout the cycle—that typical of the 19th day normally—and œdema of the stroma 14% of the women had side-reactions, such as nausea and abdominal pain, which were sometimes severe enough to cause them to abandon their tablets, but which were relieved by antacids in 90%, and by a placebo in 65%, of cases The effectiveness of the drug as a contraceptive is shown by these figures

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The Widdicombe File

XLV. CAROLINE'S FUTURE

My dear Richard,

How *thoughtful* of you to send me your Uncle Tom's letter!* And how nice to see that he is still the same dear little boy I remember so well—perhaps a little younger, but then time does fly so, doesn't it? And what a coincidence that it should arrive just at a time when we are all so *preoccupied* with our granddaughter Carrie's future I do so vividly remember dear Noel sitting beside Jeremy and me on the beach in Capri (or was it the terrace in Naples?) and giving us the most wonderful advice about Sylvia That was Carrie's mother, of course And I wish I could remember what exactly his advice was but I know that it had something to do with her going on the stage And that really was many years before she went to America with Jim (her first) and started to collect those quaint little ottos (or are they oscars?) which now clutter up the house so badly

Well, poor Noel cannot afford to live in England any longer, so there was *nobody* to tell me what to do with Carrie until you sent me Tom's letter And I was just about to give her all the *wrong* advice! Because I *did* have misgivings about her wanting to do Medicine Such a noble profession, of course! But I *never* realised what a dreadful state it had got into and that you needed young women so badly Not until I read Tom's letter It used to be so different when I was young Why, I remember that *all* my doctor friends used to be intense about their work and I cannot remember *one* who wanted to play with first-stage rockets (whatever *they* are) instead of looking after his patients But I am sure that's all because today the poor boys are "dragged" and "pushed" and "bullied" and even "*cheated*" into the profession, instead of being allowed to stay at home No wonder they become such bad doctors But my dear Richard, you really must put poor Tom's mind at rest There is still Carrie, and some of her friends, who really *want* to do Medicine and you cannot imagine how wonderfully intense they feel about it and with so many lives entrusted to them, let us hope that they always will do (And surely there must be a *few* young men left like that!)

But then, I must confess to you, there *was* also this question of marriage that kept worrying me - Not that Carrie ever consults me or Sylvia about things like that but watching our own Dr Misgust, who comes to write up Jeremy for his sleeping-pills, I did become quite perturbed Because the poor man is always so terribly bad-tempered never a moment even to sit down, though he is really wonderfully kind and insists on sending us to the very best hospitals even when it's only a sore throat And when he did come to tea the other day I felt *so* sorry for his poor dear wife, because I am sure that she wasn't nearly so interested in cancer and yellow fever as Jeremy and I and the Vicar and Mrs Appleby and they do have tea together quite often But I see now how different it will be for Carrie After all, it *is* quite likely that she will marry a doctor and then, as Tom says, she and her husband will be able to forget about their marriage now and then and talk "shop" And when I think of all my friends and their husbands who have had *nothing* to talk about for the last thirty years, and when I have to listen to Jeremy who still talks tinned fruit (although it's five years now since he retired) every time I want to talk to him about something *interesting*, well, isn't it going to be fun for Carrie and her husband to talk the *same* "shop" to each other any time they feel like talking? But, of course, Carrie might not marry a doctor only why does Tom say that if she didn't, it would have to be a poor half-wit? Not that I think that all husbands need to be intelligent, or even bright but it is really distressing to think that there are only a few Englishmen left who are able to grasp that being a doctor one cannot *help* learning

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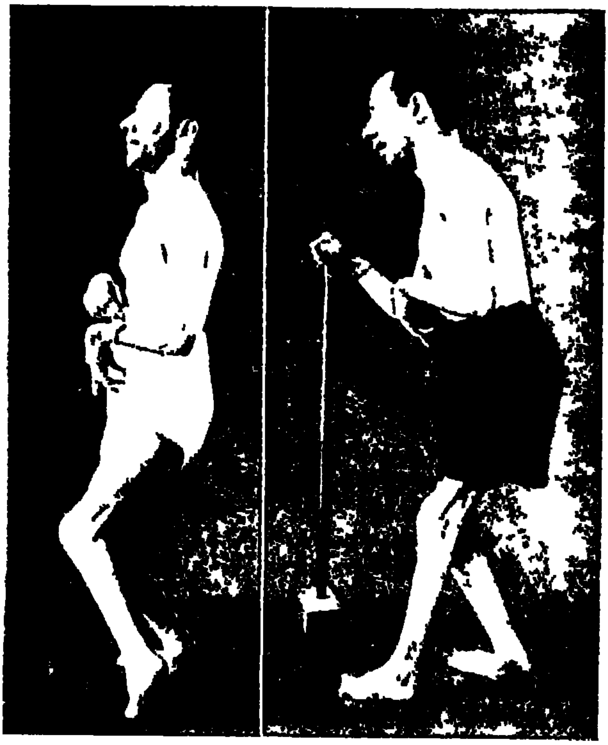
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* Reproduced in the Widdicombe File, March 1

Well, whether one marries a doctor or not, Tom is so right in saying that a husband shouldn't be " just something handy around the house ", as most husbands are nowadays And how nice that Carrie's husband will never have to be just that because, with other things on her mind, he could almost *run* the house (with a little supervision at first) and wouldn't that be fun for him, and, I'm sure, so much better for the house too?

And thinking of husbands made me think of children because, however intense Carrie might feel about her Medicine and about her husband, in this modern world a double life like that will hardly be enough to keep an intelligent young woman like her fully occupied So she will have plenty of children And when I read in Tom's letter about all the *horrible* brainwashing and bullying that goes on in the schools, I thought to myself that we really must make quite sure that at least they have a nice and interesting homelife And if Caroline can go out to work and relax, and doesn't have to stay at home and just look after the children day after day after day, and year after year after year, and get grumpier and grumpier, and wearier and wearier, and duller and older all the time, well, then that won't be too difficult Of course, Jeremy and I, and Sylvia and Ron (her present and fifth), and even perhaps her husband's parents and grandparents will all have to give her a hand but won't it be fun for the children to have a real *family* about, and not just a lot of old relatives like most other children And you cannot imagine, my dear Richard, how much we are all looking forward to that because I don't think you young doctors realise that, now that you keep us old people so wonderfully fit, doing nothing does get a little monotonous And though I may not have been much good at educating my own children, I did always take the best advice (like Noel's and Tom's), and I did always try to learn by watching other children whose parents did a lot of educating (And that wasn't usually difficult, because they always came to our house whenever they could get away from their own homes)

Well, when I told Carrie all this, she said that, though it was a *great* help to get all this encouragement from such an experienced person as Tom, not all doctors were as tolerant and farsighted as he, and that some were positively *obtuse* and didn't like the *idea* of what they called " female competition " So I made a point of asking our Dr Misgust next time he came and he got so excited that he spent a full five minutes (which he could have spent examining his next three patients) telling me that women were all right to look after women, but that they just didn't *understand* men And I said that was exactly what I thought would make doctoring so nice for Caroline because men, who do understand men, don't seem to care for them a bit and it must be so much nicer to look after patients one likes And that made Dr Misgust quite angry at first (because he hadn't thought of it before) and he said that it showed how illogical women were (But, of course, women are much more logical than men because when they do something for the sake of logic they usually have a good reason of their own as well) In the end he cheered up quite a bit and before he left he had to admit that Medicine hasn't been the same since women were first allowed to qualify And when I began to think of all the wonderful discoveries doctors have made since then (even if not *all* were women) I really felt quite proud

After this all that kept worrying me was the bit in Tom's letter about filling in forms and " dashing to the four corners of the Realm " to try and find a vacancy But there again, I said to myself, with all those great universities and hospitals absolutely packed with men, and men being so logical, it couldn't be as bad as all that And it wasn't Because last week Jeremy went to see Sir Harold Vymme in Harley Street for his quarterly blood-pressure and after he had had it all checked and adjusted I told Sir Harold about Carrie wanting to study Medicine at St Nicholas' (which is practically run by Sir Harold's secretary) Well, at first he wasn't a bit hopeful and I must confess to you, my dear Richard, that when he started telling us in his wonderfully melancholy voice about all the poor young men who wanted to get in, and about them having to earn a living later on, and about having only one vacancy for three, and whether I thought it fair to keep one of them out to get Carrie in well, I suddenly felt quite ashamed of myself And I said I would call in Carrie and put it all to her in this way, and that I was sure that when I had done that, she would want to change her mind And so I did call in Carrie but it wasn't Carrie who changed her mind It was Sir Harold Because just as I was coming to the bit about those nice young men wanting to get in (and the tears began to roll down Carrie's cheeks) Sir Harold suddenly remembered that it was just remotely possible that he may have forgotten about one particular vacancy And that brought just the faintest little smile to Carrie's face and I know it's not for me to say, but *she really does look so pretty every time she does that* Her mouth opens just a tiny bit and but I mustn't stray from what I was saying Or rather, I wasn't saying very much by then, because the more Sir Harold thought about it, the more sure he seemed that there was, in fact, a place still open But of course he was quite firm with Carrie and he said that she would have to come and see *him in his office first And Carrie said that she* would love to go, even if there was not the slightest chance of her staying on But by then Sir Harold was quite positive that there would be And Tom really mustn't be too unfair on men (even if they are only logical most of the time), because this only happened last week and today Carrie telephoned and said that it was all arranged for her to start at St Nicholas' next autumn And whatever happens, my dear Richard, you really *mustn't* let Tom chain himself to the Palace railings That was all right with only a king living there, but now that even *that* job has to be done by a young woman, it really wouldn't be fair But do thank him again for all his wonderful encouragement and I am letting Mrs Appleby and all my friends read his letter so that they can all benefit from his advice

Goodbye for now, my dear Richard, and give my love to all the family

Your affectionate old friend,

MARY WORTHINGTON

Conferences

HORMONES AND ATHEROSCLEROSIS

A conference sponsored by the endocrinology and heart sections of the National Institutes of Health was held from March 11 to 14 at Brighton, Utah, under the general chairmanship of Dr Gregory Pincus (Worcester, Mass)

Cholesterol Metabolism

Prof Sune Bergstrom (Lund), who considered the influence of intestinal flora on the excretion of cholesterol and bile acid, showed that hypothyroid rats excrete almost pure cholic acid, whereas *hyperthyroid rats excrete mostly chenodeoxycholic* acid This difference may be due to stimulation of bacterial floral activity by the thyroid hormones He agreed that, although the liver is the primary site for cholesterol degradation, all tissues have the capacity to degrade cholesterol into bile acid

Dr G S Boyd (Edinburgh) showed that in rats thiouracil has an extrathyroidal effect in elevating plasma-cholesterol Triiodothyronine and tri- and tetra-iodothyroacetic acids cause selective increase of the oxygen requirements of isolated myocardium, and the administration of tri-iodothyroacetic acid to hypercholesterolæmic rats reduces both plasma-cholesterol and lipid deposition in the aorta

Dr J E Rall (Bethesda) demonstrated that low concentrations of circulating thyroxine are bound between the alpha-1- and alpha-2-globulin fractions, but that higher concentrations are apparently attached to albumin Sex hormones can influence thyroid activity by altering the protein-binding capacity and thus altering the concentration of circulating free thyroxine

Arterial Wall and Cholesterol Transport

No critical level of blood-cholesterol has been observed for the development of experimental atheroma, and hypercholesterolæmia induced by alloxan or detergents is not often followed by atheromatous lesions, these observations, and the irregular distribution of atheromatous lesions, do not accord well, in the opinion of Dr R L Holman (New Orleans), with the filtration theory of the pathogenesis of atheroma He emphasised the importance of the arterial wall, indicating that atherosclerosis is a gradually progressive process with well-defined histological stages

Dr N T Werthessen (San Antonio) showed that the accumulation of cholesterol in the isolated perfused aorta is directly related to the initial concentration of cholesterol and to the glucose content of the aorta

Dr D B Zilversmit (Memphis) has shown by tracer studies that all phospholipids have a higher specific activity in the aorta than in the plasma He believes that excess phosphatide in the aorta is probably due to local synthesis It is possible that once the process of arterial lipogenesis is set into motion, reduction of hypercholesterolæmia will have little effect

Dr Leon Hellman (New York), who has cannulated the left thoracic duct in humans, reported the results of simultaneous analyses of the plasma and lymphatic lipids In normal people and in hypercholesterolæmic non-lipæmic patients, the plasma specific activity of ^{14}C-labelled free cholesterol is greater than that of esterified cholesterol, but in hypercholesterolæmic hyperlipæmic subjects the specific activity of ^{14}C-labelled ester cholesterol is greater This might suggest the possibility of a defect at the intestinal level of absorption. Dr Hellman indicated that the fall in plasma-cholesterol following corn-oil administration is more directly related to excretion of sterols than to that of bile acids

Hormones and Experimental Atherosclerosis

Dr David Adlersberg (New York) showed that cortisone and prednisone increase plasma-free-cholesterol, beta-lipoprotein cholesterol, and plasma-phospholipids The combination of cortisone with cholesterol feeding causes greater hypercholesterolæmia but less atherosclerosis in animals fed cholesterol alone He suggested that this may be due to a decrease in arterial permeability produced by cortisone, and in support of this the simultaneous administration of hyaluronidase increased the degree of atherosclerosis

Dr S O Byers (San Francisco) reported that rats which were intermittently stressed by contact with an electrical charge at varying points in their cages, and were therefore very active physically, had no change in the plasma cholesterol or phospholipids, but had shortened clotting-times when compared with a control group

Dr Marmorston (Los Angeles) reported that in dogs a single injection of corticotrophin (A C T H) resulted subsequently in a greater hypercholesterolæmic response to cholesterol and thiouracil feeding than if no corticotrophin had been administered Extensive atheroma developed in these dogs throughout the vascular tree and some even had cerebral hæmorrhage A flaccid paralysis was observed in other dogs, but it was not clear whether this was related to the cerebrovascular lesions

Dr R Pick (Chicago) believes that a decrease in the cholesterol/phospholipid ratio is more closely related to the experimental regression of atherosclerotic lesions in the chick than any other lipid measurement All her experimental observations on the chick have emphasised that the aorta is more sensitive to the production and reduction of lipid-rich lesions than the coronary arteries

Dr R H Furman (Oklahoma City) reported a case of biliary cirrhosis in a woman, aged 30, in whom the plasma-cholesterol increased to 3000 mg per 100 ml but the cholesterol/phospholipid ratio remained less than unity At necropsy there was atherosclerosis in the aorta but the coronary arteries were healthy

Hormones and the Blood Lipids

Dr Joseph Shifter (Philadelphia) reported further studies on a lipid-mobilising factor that can be demonstrated in the posterior pituitary of hogs and is apparently independent of known pituitary hormones Parenteral injection of lipid-mobilising factor produces hyperlipæmia in the systemic circulation in the presence of liver damage, but with a healthy liver this hyperlipæmia is confined to the portal circulation

Dr R H Roseman (San Francisco) reported that the plasma-cholesterol levels were increased and that the clotting-times were decreased in accountants when they were undergoing the stress of having to balance quarterly accounts

Dr David Adlersberg (New York) emphasised the association of acute pancreatitis with hyperlipæmia and felt that the role of glucagon in the regulation of lipid metabolism needed considerable clarification Dr G S Boyd (Edinburgh) did not observe destruction of the alpha-cells following cobalt chloride administration, which resulted in a rise in the plasma-cholesterol and a fatty liver in his rabbits Dr E Strisower (Berkeley) reported that the concentration of high density lipoproteins decreased after the administration of very large doses of desiccated thyroid, thyroxine, and triiodothyronine to euthyroid patients Dr M F Oliver (Edinburgh) had also observed a decrease in the alpha-lipoprotein concentration with large doses of thyroxine and triiodothyronine, but he felt that this might be a dose effect since the alpha-lipoprotein level was actually increased with smaller doses of these thyroid hormones

Dr Howard Eder (New York) reported that a low dose of methyl testosterone did not necessarily produce much change in the total cholesterol in the plasma, although the beta/alpha-lipoprotein ratio is increased Similarly, he had observed a decrease in the beta/alpha-lipoprotein ratio without any very significant change in plasma-total-cholesterol following the administration of certain weak œstrogens He raised the question whether a compound which allowed a change in the lipoprotein ratio but not in total cholesterol was of any value in influencing atherosclerosis

Clinical Biological Relationship

Dr A R P **Walker** (Johannesburg) emphasised the rarity of coronary-artery disease in the Bantu Cerebral atherosclerosis and hypertension are common and often severe The principal differences from Western nations are in the diet and physical activity There is a higher concentration of unesterified fatty acids, greater fibrinolytic activity, and greater œstrogen excretion in the Bantu than in the White A third of adult male Bantus had gynæcomastia, but as yet there is no definite correlation with the incidence of liver disease Liver disease probably contributes to the rarity of atherosclerosis in the Bantu, but this is probably mostly determined by the diet

Dr M F **Oliver** (Edinburgh) indicated that various thyroid analogues decreased the plasma-cholesterol without apparently increasing the basal metabolic rate, but so far these had proved to be unsuitable since the cholesterol-lowering effect could not be maintained beyond a few weeks and angina was aggravated in a quarter of his patients Following the clinical trial of several weak œstrogens, he concluded that it was not yet possible to dissociate the cholesterol-lowering action from their feminising effects (Dr **Roger Robinson** [Worcester, Mass] and Dr **Victor Drill** [Chicago] had found the same) Although the administration of ethinyl œstradiol for two and a half years to 50 men with myocardial infarction had reduced the plasma-lipid levels, there was no difference in morbidity and mortality from further coronary episodes between these men and another 50 receiving lactose

Dr J **Stamler** (Chicago) reported similar results from a group of about 100 men who had received 'Premarin' (conjugated œstrogens) over a three-year period There was no definite evidence, therefore, that the long-continued reduction of the plasma-lipids improved the prognosis

NEOPLASIA

A **conference** on Neoplasia organised by the postgraduate medical education committee of the University of Glasgow and the Royal Faculty of Physicians and Surgeons was held on March 26–28

General Concepts

Dr **Philip Peacock** said that the first rational idea of causation was Percival Pott's observations on chimney-sweeps' cancer of the scrotum Tumours arise in all animals, but some tumours common in man seem to be rare in other animals Theoretically cancer can start from one cell, but the earliest case which Dr Peacock has seen was multicentric In this case, in addition to the definite neoplastic foci there were areas of retained sebaceous secretion, and the possibility of this being carcinogenic must be considered, especially in view of recent suggestions that cholesterol is a carcinogen Perhaps cholesterol can be transformed into methyl cholanthrene Except in a few industrial cases the cause of carcinoma is unknown, and even where the carcinogen is recognised, the final process remains to be discovered Contaminants of so-called carcinogens may be the active agents

Some virus-induced tumours regress spontaneously, the reason for this may be in the hereditary transmission of the tumour, and an additive factor may be involved Dr Peacock's concept of neoplasia is that cancer is an alternative mode of existence for a cell which is threatened by death It may be due to imbalance of cell constituents

D N A

Prof J N **Davidson** reviewed the knowledge of cell substances, notably those of the nucleus Of these, desoxyribonucleic acid (D N A) is the most important The amount of D N A in the cell is remarkably constant in different organs except the liver, where it is increased Many tumour cells have more D N A than normal cells D N A may actually alter the characteristics of cultures and even of organisms For example, D N A from a mutant added to a sensitive culture will produce mutant cells in the culture D N A from phage may alter *Escherichia coli*, to produce further phage

Endogenous and Industrial Tumours

Dr B D **Pullinger** said that some tumours now considered endogenous may eventually be removed from this group by further research Squamous carcinoma of the lung may or may not be endogenous, but it seems likely that neoplasia of the scrotum is exogenous, as it occurs mainly in the lower social classes and the agent can probably be washed off The virus tumours of animals are difficult to classify Some tumours—notably polyposis coli and retinoblastoma—are hereditary Some—notably carcinoma of the breast—appear to be familial

It is impossible to study hereditary tumours in man, because of their irregular breeding, but it may be possible to produce tumours in animals which are highly inbred The reason for tumour formation may be senescence of the cell or the presence of internal substances which irritate the cell Recently many mammary tumours have been associated with cholesterol deposits Cholesterol has caused carcinoma in the bladders of mice It has recently been shown that carcinoma can be produced locally by the injection of œstrogen

Dr A T **Doig** spoke of industrial cancer The possible factors involved are tar, pitch, shale-oil, asbestos, X rays, ultra violet rays, arsenic, and chromates Radium and radioactive materials have become important Latent periods may be long In some industries non-carcinogenic materials may be substituted, and in some the process can be properly screened Dr Doig made a strong plea for the notification of all cases of possible industrial cancer, so that the conditions of work might be inspected

Reticulo-endothelial System

Dr R I **Shaw Dunn** classified tumours of lymphoid tissue into (1) Hodgkin's disease, with subdivisions of typical, atypical, Hodgkin's sarcoma, and Brill's disease, (2) lymphosarcoma, which may be small- or large-celled, (3) lymphoreticulosarcoma, (4) reticular cell sarcoma, and (5) miscellaneous

Dr A **Brown** dealt with the clinical picture of "reticulosis" Leukæmia is merely a symptom of several different diseases There has been a gross increase in this condition after atomic bombing, and in radiologists, but its incidence has also increased in the general population over the same period The prognosis of these diseases of the reticulo-endothelial system is poor, the average survival being two and a half years—though patients with Hodgkin's disease may survive for several years and those with chronic leukæmia for up to twenty years The management of these lesions is non-specific X rays may be used at the local site of a disease, chemotherapy is generally reserved for radioresistant or generalised lesions Dr Brown favours nitrogen mustard by injection, but recent results with tretamine (T E M) and busulphan ('Myleran') are poor Anti-metabolites, such as folic-acid antagonists and purine derivatives, are giving some beneficial results

Regional Cancer

Prostate

Mr W B **Stirling** said that in prostatic cancer the serum-acid-phosphatase is increased in 90% of cases Only 5% of the patients are suitable for radical prostatectomy, the rest are treated by stilbœstrol Without treatment, the average duration of the disease is fifteen months, with 9% five-year survivals, after stilbœstrol the average duration is forty-five months, with 27% five-year survivals Adrenalectomy and hypophysectomy yield poor results

Liver

Prof J W ORR (Birmingham) pointed out that, in Africa, primary cancer of the liver is found in 1% of all necropsies, compared with 0 1% in Europe In South China and in Indonesia it is common in the natives but rare in Europeans The age and sex distribution is explicable by the survival-rates of these populations Race seems to have little effect, the Africans in America have lost their tendency to primary liver cancer This uneven incidence of carcinoma of the liver may be explained by a dietetic deficiency or by a toxic factor Primary liver tumours are not common in animals, but can be induced by butter yellow and similar substances The tumours that develop are similar to the primary tumours in man It seems likely that carcinoma develops on a process of regeneration

Stomach

Prof C F W ILLINGWORTH remarked on the poor results of the treatment of carcinoma of the stomach—a disease which now causes the death of 300 people a week in the United Kingdom The five-year survival-rate is only 2 7% in all diagnosed cases, and 12% in those who have had gastric resection The ætiology is unknown, and tumours cannot be produced in animals by feeding carcinogens It is unlikely that gastric ulcers lead to cancer in more than 5% of cases of ulcer In treatment radical total gastrectomy is unsatisfactory, and partial gastrectomy is probably best. Exfoliative cytology does not add many to the cases diagnosed by other means Routine test of the stool for occult blood may be a useful screening-test for gastric cancer

Thyroid

Dr E M MCGIRR said that cancer of the thyroid gland accounted for only 0 4% of deaths from malignant disease At all ages it affects females more than males There are three main types (1) differentiated (papillary follicular, and Hurthl-cell adenocarcinoma), (2) non-differentiated, and (3) miscellaneous Surgery has not given very good results, and radioactive iodine is suitable for only 10% of the cases

FREEZING AND DRYING

THE second international symposium on freezing and drying was held, under the auspices of the Institute of Biology, in London on April 1 and 2

General Topics

Dr H T MERYMAN (U S.A) discussed the mechanical and biochemical changes during freezing in biological systems He felt that a balance must be reached between rapid cooling (in which mechanical damage is maximal) and slow cooling (in which biochemical damage is maximal) The use of additives, such as glycerin, may be rendered unnecessary by uniformity in freezing and thawing

The paper by Prof N KALABUKHOV (U S S R) was read by Dr A U Smith It dealt with the problems of undercooling, freezing, and vitrifying whole animals Experiments were described in which bats were undercooled to −5 to −7°C, and survived storage at these temperatures for periods up to several days At −4 3°C the heart-rate of bats was about 8 beats a minute, compared with the normal rate of 400

Microorganisms

Dr W J SCOTT (Australia) discussed the role of protective agents in storing freeze-dried bacteria One cause of death is the intracellular reaction of carbonyl with amino groups—known as the browning reaction. This occurs in dried preparations, and the water formed during the reaction accelerates the process Glucose or ribose in the medium improves the viable count immediately after freeze-drying, but exerts a deleterious effect on stored organisms Their corresponding reduction compounds (sorbitol and ribitol) give protection without facilitating the browning reaction Addition of aminoacids to the freezing-mixtures to compete for the carbonyl groups is another means of protection, Lysine and sodium glutamate have been found useful in this respect Along similar lines sulphur dioxide, which reacts with ketone and aldehyde groups, exerts a protective action

Dr R. I N GREAVES described some factors which influence the stability of freeze-dried cultures, with particular reference to the browning reaction Dried cultures have been boiled to assess the effects of various drying media on their stability when stored for long periods Glucose in the medium gives high initial survival-rates, but the dried cultures are very heat-sensitive The greatest resistance to high temperatures was found in media consisting of 5% sodium glutamate in 5% dextran solution

Prof D GRIEFF (U S.A) talked of the effects of freezing, low-temperature storage, and drying by vacuum sublimation on the activities of viruses and cellular particulates Viruses showed less loss of infectivity when they were dried from the vitreous, rather than the crystalline, state The activity of mitochondria, measured by their capacity for oxidative phosphorylation, was better retained after slow than after rapid freezing This is possibly related to the preservation of the integrity of mitochondrial membranes

Miss B L BRADY described observations on the freeze-drying of yeasts, which is used as an ancillary method to maintain the national collection of yeast cultures With freeze-drying little difference is noted between the survival-rates of sporing and of non-sporing cells, and between haploid and diploid organisms There are generic differences in survival-rates After freeze-drying no change has been noted in vitamin and aminoacid requirements of the yeasts

Grafts

Commander G W HYATT (U S A) spoke of experience in maintaining a bank of freeze-dried human cadaveric tissues for use in surgery Skin, dura, fascia, bone, and arteries are removed aseptically from selected sites The tissues are placed in a medium containing serum and then freeze-dried at 4°C for six weeks, at the end of which the moisture content has fallen to 2 7–3 5% The materials are stored in sealed vessels at room temperature until needed. Bone stored for up to five years has been used successfully

Prof C G ROB described the experience of his surgical unit with freeze-dried arterial grafts Of the last 394 arterial reconstructions, 178 were carried out with homologous tissue transplants Frozen arteries were used in 78 of these, and freeze-dried arteries in 100 The two types of material take equally well The criterion of success is the absence of thrombosis, and anticoagulant drugs are an essential part of postoperative routine.

Colonel F HENAFF (France) discussed freeze-drying associated with corneal grafts The freeze-dried corneas are undoubtedly non-viable, but both full-thickness and lamellar grafts have successfully been carried out with homologous and heterologous (dog) material

Dr A S PARKES discussed the freeze-drying of viable grafts Rat ovaries are good test material because when they are grafted they become physiologically active after a few days Frozen ovaries retain their activity for at least two years when stored in 15% glycerin at −79°C At this temperature viability has been maintained although the tissues are effectively dry, because their water is in the form of ice The problems are how to remove the ice, and what to do with the residual glycerin High concentrations of glycerin are toxic at room temperature This is therefore an unsuitable component of freeze-drying media An ideal protective agent would protect against freezing, be non-toxic, and sublimate with ice during the drying process To this end, methanol has been tested on rat ovarian tissue in freezing experiments Viable grafts have been obtained after ovaries have been kept for a few hours in methanol at −20°C

In England Now

A Running Commentary by Peripatetic Correspondents

I SPENT most of Easter in a new way—on a protest march A new experience for one so apolitical A most impressive experience So many sorts and conditions of men, all trudging along in the foul holiday weather to Aldermaston I couldn't stay the whole course, for family reasons, but managed Good Friday and the Easter Monday march to Aldermaston itself The skiffle groups and the beards weren't surprising, there were plenty of obvious vegetarian, teetotal, sandal-wearing oddities, but the real surprise was the number of normal, ordinary, shabby people, the kind you see on a bus or in your surgeries, far outnumbering the peculiars The profession seemed a trifle thinly represented, though I had two medically qualified companions on Friday and one on Monday

Thirteen miles is a fair stretch, and there were many footsore blistered plodders by the end An efficient-looking motorcyclist with a Red Cross flag was in evidence, and I saw one girl with actually bleeding feet waiting for his attention The organisation was extraordinarily well done and not obtrusive The marshals wore tangerine armbands and appeared at intervals, shepherding the stragglers and keeping the column more or less in triple file It seemed endless, winding along over hills and bridges—you could see the big black square banner at the head, but not the tail, just a three-deep switchback of people who felt strongly enough to be there There was a policeman every 100 yards or so, friendly and smiling, but efficient—a collie, one felt, who would stand no nonsense from his flock but who had their interests at heart The considerable traffic wasn't allowed to jostle us too closely and often had to wait

When we got to the precincts of Aldermaston we marched in silence—fairly strictly observed for the most part, though there were some inveterate chatterers behind us Aldermaston seemed a blend of science fiction and normal life The high wire, dogs, armed guards, and some very functional buildings all fitted in, but there was a lake, and some blocks of buildings in contemporary colours like modern flats, which looked out of place We marched round it, silent, a bit grim, tired and cold There were thousands of spectators, nearly all were friendly, and many, from Trafalgar Square to Aldermaston, smiled and clapped and shouted encouragement Some of course just "gawped" indifferently, but the overwhelming impression was of support

The journey home took *hours*, but for all that it was a satisfying way of spending Bank Holiday Next morning my five-year-old said "Did you stop them?" I couldn't think what he was getting at and said ungrammatically "Stop who?" "The Government," he said, "from making H-bombs" I had to confess we hadn't—yet

* * *

Some years ago we designed a controlled trial to assess the effect of winter chemoprophylaxis on chronic bronchitics in a community Only subjects who were severely affected were included and they were given either real or dummy tablets of a certain drug according to the dictates of our statistician

Last year, when we revisited the community to invite its members to take part in a further investigation, we were dismayed by their apparent reluctance to cooperate with us again We soon discovered that their hesitation was due to apprehension lest we were about to issue more tablets, for, while we *had* found the results of the previous trial statistically insignificant, the subjects themselves had carried out their own analysis in the years that followed and come to a highly significant conclusion almost all who had taken *any* of our tablets were now either very much worse or dead

* * *

Archie White had been a sore trial to many of us A young man with a duodenal ulcer, he had fallen in with a gang of car thieves and as a result spent three months in gaol Unimpressed by this experience he made further unsuccessful excursions into the illicit car trade and again enjoyed Her Majesty's hospitality for a year Soon afterwards he appeared at my clinic and I sternly warned him that he must mend his ways or he would find himself breaking stones in penal servitude It was clear that Archie found this prospect unattractive and he promised to abandon his old associates Later I heard that he had a job with a firm of road contractors

I saw nothing more of him till last week Held up in a traffic block I was idly gazing at a group of workmen who were repairing the road when I saw the figure of Archie White bending down to pick up a large cobblestone He looked up, recognised me immediately, and reaching for a hammer proceeded with a rueful shake of his head to break the stone As I drove past he favoured me with a splendid wink and a touch of his cap

* * *

I always enjoyed walking on stilts Since I reached an age when it no longer seemed normal to possess a pair I have longed for the time when my son would be old enough to own some

Recently I bought a pair They were made of red tubular steel and were much more handsome than the home-made ones I had used in my youth I hid them in the cellar to await his birthday, but I was so excited about them that I found it difficult to keep them there I admit that once or twice, after he had gone to bed, I fetched them and walked them round the drawing-room After all, I had to make sure of my superiority before he received them

Two days before his birthday my son announced that he was so glad he was receiving a clockwork train for his birthday I remembered in horror that, months before, I had promised him a train A train there would have to be

Now the stilts must remain in the cellar until Christmas I long for them more and more, but will content myself with nocturnal walks on them round the garden on summer evenings Perhaps it is better so Toys are best when they are not shared, and I never was enthusiastic about clockwork trains

* * *

We thought we finally decided to buy the house because it had two gates We had always hated backing the car into the road and at last we had a drive encircling a green lawn We kept our gates open and drove in at one and out of the other But patches of brown appeared on the lawn and ruined its appearance Investigation disclosed that every passing dog entered one of our gates and left by the other, leaving his mark on the lawn in passing When, for experimental purposes, we left one gate shut, no dog entered It had not occurred to us that dogs would share our liking for double gates Their motives must be purely psychological A dog does not need to exit in reverse through a single gate

We decided that our motives were psychological too We now keep one gate closed and through the other we reverse the car as before What we really like of course (and this must be the real reason why we bought the house) is looking out of the window on to a green lawn In that, at least, we differ from the dogs, except our own, who fortunately shares our respect

* * *

News from School—On Friday there was for me the great event of the term, particularly as there were only four other dinner jackets there It was in the gym of a school at ———— It started at 7 30 sharp At that hour all the males were sitting self consciously round the walls At 7 31 the females trooped in, not quite in crocodile, but possibly in height order from the front After we had sat there for five minutes more, with the mediocre band playing moderately hard, I leaped to my feet, singled out a female on the other side, and gave a demonstration *of the Gay* Gordons with her She had only done it once before *After* that all the earnest, dark-suited, open-neck-shirted boys surged to thei feet as one, and there was a hubbub of intelligent conversation My partner thought I was a sort of Carruthers and I did not disillusion her We danced until 9 45, when my house-master had ordered us to start back By that time I knew her first name, just *She* doesn't know mine I hope that all she will remember is the brilliant conversation, the unobtrusively perfect dancing, and the perfect breeding of the charming young gentleman who whisked her round the floo so effortlessly that March night She told me her father had forbidden her to rock and roll, so we rocked and rolled After that we parted, she with a wistful look in her eye

Letters to the Editor

A BALANCED HOSPITAL COMMUNITY

SIR,—A consultant colleague greeted me on the morning of April 5 with the remark, "This man McKeown is talking sense about hospitals" That sentiment will surely be echoed by all who have studied the needs of our hospital service I write, however, to remind your readers that the views so ably supported by Professor McKeown's figures for Birmingham were one of the basic reasons for introducing a regional and group hospital service Experts writing as early as 1938 in the prize-winning article on a hospital service, The Walton Plan,[1] made a plea for

> " real general hospitals which will admit all kinds of cases including infectious fevers, tuberculosis, maternity, mental disease, and sick children. The hospital will have 1000 to 1200 beds and serve about 100,000 people. A general hospital of this kind will be able to care for a large number of chronic cases without exhausting the interest of the staff There is a great tendency to exaggerate the degree of infirmity of those who are merely old as under the scheme there will be no acute hospital, so there will be no need for the corollary, the chronic hospital"

This conception became the basis of all discussions on future hospitals, and writing in 1942 in *Health for All* I was able to "make another assumption, that all hospitals in a socialised service will be general hospitals taking every type of case" Indeed one had in mind and has always advocated a system of general district hospitals which would assume the primary responsibility, in the closest cooperation with the general practitioners, for all the hospital and specialist care needed by its unit of population It could not effectively deal with everything on the spot, but it could take the responsibility for deciding how each case should be dealt with most efficiently (from the sick person's angle) either because it had the resources or could direct the patient to the necessary resources (This is of course the principle on which our group laboratories which give an open-access service operate, with all the reference laboratories to take the more unusual cases from them)

In short, the theory of twenty years is shown to be correct by general experience and now by Professor McKeown's excellent article But why do we seem so far from the ideal? Is it the profession which has not realised this need and so has not put the right pressure on the lay and financial authorities to amalgamate and reorientate our hospitals? Are we still bound by ideas nearly as old as our hospitals (more than half of them one hundred years old) and so unable to advise our lay committees with the authority that would make them move? I hope Professor McKeown's article will set the ball rolling

Kingston Hospital,
Kingston-upon-Thames, Surrey

D STARK MURRAY

"THESE DYING DISEASES"

SIR,—Dr Ambrose King's thoughtful article on venereal diseases (March 29) is timely and shows clearly the difficulties which are rapidly approaching in the present venereal-disease service In spite of Dr King's rosy picture for the future of this branch of medicine, the hard fact remains that the young man with at least 35 years of active life in front of him obviously does not consider that venereology is for him, and the service as we know it is slowly but inevitably disintegrating The time has surely come for fundamental reorganisation in order to have a workable scheme ready for the care of these patients when the present system breaks down.

Venereology differs from most other specialised branches of clinical medicine in that it is specialisation in a group of disease-processes, whereas other specialists are concerned with all types of illness and alteration of function which may affect the part of the body in which they are particularly interested The difficulties attendant upon specialisation in a disease have recently been seen with tuberculosis, and the same trend is happening with venereal disease. It is probably this and the relatively small number of new cases seen at each clinic that discourage recruits, rather than such factors as hours of work, &c.

From Dr King's figures, the majority of the cases attending the clinics are not suffering from venereal disease, the cases with non-specific urethritis are now the major problem, and these are in need of general medical investigation and care Most cases of late syphilis are treated by the physician specialising in the organ mainly affected and not by the venereologist In the same way, the treatment of all these patients could be taken over by the appropriate specialist. Patients presenting with skin manifestations could be treated by the dermatologist, congenital infection by the pædiatrician, genitourinary discharge by the genitourinary specialist or the gynæcologist, non-specific urethritis by the general physician, and so on This is virtually what has happened in the case of tuberculosis

Two problems remain one is the patient with a discharge or fear of infection, and the other is preventive measures With regard to the first, since 1948 everybody in this country should have his own family doctor, and it is to him that the patient should go, being referred by the practitioner if necessary to the appropriate specialist With regard to the control of venereal disease, notification, with due safeguards for secrecy, could be introduced by appropriate legislation so that control can be undertaken by the department best equipped for doing this—namely, the medical officer of health and his team

Thus, with the inevitable running down of the venereal disease service, the duties formerly undertaken by the venereologist would gradually pass back into the medical fold and the stigma of "special clinics" and special wards would disappear

These ideas are put forward not in any spirit derogatory to the present venereologists but as a basis for trying to deal with a problem which must be tackled within the next few years when the number retiring exceeds the number of recruits

Oxford.

H. R. VICKERS

CONSULTANT DISTRIBUTION

SIR,—It is true, as Dr Joules says (April 5), that facts are gradually emerging which tend to show some inequity of consultant distribution in the country It is not true, as Dr Joules imputes, that the medical profession has failed to strive for an increase in consultant establishments Indeed, even in Dr Joules' own region (which, according to details given on p 748 of your same issue, must be one of the most heavily staffed in the country), there has been considerable agitation in the medical committee to secure a review of the consultant establishment.

It seems that one of the objects of Dr Joules' letter is to imply that those boards with the lowest consultant staffing ratio may have been influenced by "very powerful medical advisory committees" The figures given in Dr Joules' letter and in your summary of a written reply by the Minister of Health on March 21 are too sparse for any proper conclusions to be drawn. For example, the table you publish makes no mention of the teaching hospital beds in the various regions, nor does it give a true idea of the number of consultant sessions in each region. Furthermore, we are given no idea of the numbers of chronic sick beds (which show considerable variation) in the different regions, or of the S H M O establishment

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[1] *Med Today*, 1939, 2, 2.

These and many other statistical details will need to be collected before we can draw any valid conclusions about the opportunities for expansion in the various regions I am, however, heartened by the fact that the figures thus far available suggest that the consultants and specialists committees have been correct in their contention that an increase in senior staffing of the hospital service is necessary

There is one important aspect of this problem on which we require much fuller information Whilst the Parliamentary answers reported in *The Lancet* give scanty information about the present staffing ratios of different regions, they give absolutely no information at all about the state of affairs at the inception of the National Health Service Is the apparently better staffing in certain areas attributable to the efforts of their regional boards since the appointed day, or is it wholly or largely due to such areas having inherited a number of hospitals which were well staffed before the N H S ? Further research may show that there has been a (relatively) greater increase in consultant establishments in the apparently worse-staffed areas On the other hand, it may be true that an area which began with a lower staffing ratio and bed/population ratio has, by virtue of its poor start, been handicapped in its endeavours to secure a bigger slice of the N H S cake

These are but a few of the many questions which occur to those medical men who seek fuller information on this extremely important subject The questions published by the chairman of the North West Metropolitan Regional Hospital Board (Jan 25, p 220), and which still remain unanswered, were framed with the object of elucidating this vexatious problem

Radlett, Herts REGINALD S MURLEY

THE COMMON COLD

SIR,—Dr Ritchie's articles (March 22) have interested me greatly I am convinced he is right in his thesis that the toxic manifestations of the common cold are caused by the enhanced virulence of the normal saprophytic flora of the pharynx I have reached an identical conclusion on the strength of experiences gathered from incidental treatment of a relatively small number of cases of common cold over the past two or three years

But you rightly point out in your annotation that there are risks involved in building up resistant strains by a widespread use of antibiotics Your readers may therefore be interested in knowing that results closely resembling Dr Ritchie's can be achieved without resort to antibiotics I have used for the resolution of the pharyngeal infection lozenges containing dequalinium chloride, which is a chemical agent active against a wide range of bacteria On some occasions a combination of this with lozenges containing chlorhexidine dihydrochloride proved more effective As indication for the systematic use of these compounds I regarded not only the developed sore throat but also dryness in the throat, the presence of which often remains unnoticed even by an observant sufferer

On two points I am inclined to differ from Dr Ritchie

One concerns the question of the virus The role and the behaviour of the virus is certainly no part of clinical observation The notion of the virus in common cold is derived from experimental work and has not yet been confirmed by laboratory techniques It seems to me that, within Dr Ritchie's thesis, the positing of the virus as the primary factor in common cold is before all else a conceptual device designed to account for the lowering of the body's resistance to its own bacterial flora, setting the stage for the unfolding of the clinical phenomenon, common cold

But epidemiological observations, such as van Loghem's in Holland, immunological considerations, and observations paying attention to psychological settings in which common cold occurs, or tends not to occur, all are somewhat difficult to reconcile with the virus ætiology of the common cold Certainly from the therapeutic point of view, in procedures such as Dr Ritchie's and my own, the virus may entirely be left out of account It is most impressive to observe how agents that are not known to affect a virus are capable of disposing of a developing cold within the shortest space of time, even within less than 24 hours, restoring the patient to full health If there be a virus, it behaves as if it did not exist

The other point is that Dr Ritchie regards as the second stage in the developing of the illness an attack by the nasal and pharyngeal flora My observation is that happenings on the nasal mucosa in common cold are distinct from those in the pharynx, and that only the pharyngeal flora is concerned in the attack

I hope later to set out my observations in some more detail and to propose an alternative theory to that of the virus ætiology of the common cold

London, W 1 JOSEPH ZELMANOWITS

SMOKING AND PEPTIC ULCER

SIR,—The following figures may be of interest in relation to the paper by Dr Doll and his colleagues (March 29) I quoted them at the recent symposium on carcinoma of the lung arranged by the N A P T

In a series of 7500 cases of peptic ulcer collected over a period of nearly ten years in the impaired lives registry of the Prudential Assurance Company, so far there have been 45 deaths certified as due to carcinoma, 18 of them were due to carcinoma of the bronchus, 17 to carcinoma of the stomach, and 10 to carcinoma in other situations This high incidence of carcinoma is not apparent in any other group of impaired lives

Since smoking has been suspected as a cause of carcinoma, both of the stomach and the bronchus, I feel that these figures, which I quoted by permission of the management of the Prudential Assurance Company, may be significant

London, W 1 E H HUDSON

ANOTHER "UNIVERSAL DIAGNOSTIC TEST"?

SIR,—I was very interested to read (April 5, p 749) about the work at the Johns Hopkins University School of Public Health on serum-mucoproteins

In diagnostic work of protein paper electrophoresis, we have certainly come to rely on the mucoprotein stain (P A S technique) to quite a considerable extent, since it is the most sensitive and easiest method of demonstrating what I have called *tissue necrosis and regeneration* [1] For the past four years the routine strips at this laboratory have been divided longitudinally into three, and a third stained respectively for total protein, mucoprotein, and lipoprotein The degree of tissue breakdown and repair (e g , in infections and trauma) is related to the intensity of the alpha-mucoprotein bands

I have associated tissue necrosis or degeneration with increase or emphasis of alpha-one-mucoprotein, and *tissue growth or regeneration with increased alpha-two-mucoprotein* The prognosis in many diseases seems to be related to an alteration in the ratio between alpha-one- and alpha-two-mucoproteins A prominent alpha-one-mucoprotein band carries a bad prognosis Alpha-one-mucoprotein is emphasised in many cases of hæmolytic diseases, heart-failure, steatorrhœa, malignant hypertension, some malignant diseases, some virus diseases, &c , and approaching death *Alpha-two-mucoprotein* is emphasised in childhood, pregnancy, neoplasm, arthritis, infarction, trauma, and renal disease

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[1] Dagnall, P *Clin chim Acta*, 1957, 2, 391

The interesting points mentioned in your note are too numerous to discuss here There are some abnormal beta- and gamma-mucoproteins—e g, the unusually staining beta-mucoprotein in myxœdema, the gamma-myeloma-mucoproteins, and the mucoproteins of miscellaneous fluids, such as urine and pleural, peritoneal, and synovial fluids

Rewarding observations may also be made by relating increases in mucoprotein to the appropriate portion of the paper stained for total protein—e g, in rheumatoid arthritis the increase in alpha-two-mucoprotein is in excess of that shown on the strip stained for total protein These latter findings may prove to be of greater diagnostic importance than changes in the mucoproteins themselves

Kingston Hospital,
Kingston-upon-Thames, Surrey
Phyllis Dagnall

NEW METHOD OF PHENOBARBITONE ADMINISTRATION

Sir,—I cannot agree that Dr O'Connor (March 22) has really demonstrated anything

The mean daily dose of phenobarbitone in the control series was gr 2 8 daily, and with 'Spansule' treatment gr 5 8 The toxic effects noted with the patients receiving regular phenobarbitone were mainly subjective ones, which must be very difficult to evaluate in psychotic patients It would be reasonable to suppose that such symptoms might disappear if the dose of ordinary phenobarbitone were doubled This essential control is missing

Dr O'Connor must be unaware of the study by Butler et al [1] These workers showed that in man there was no significant difference in blood levels of phenobarbitone between divided daily doses of regular phenobarbitone and phenobarbitone in spansule form, when equal doses of the active drug were given For a drug which is excreted as slowly as phenobarbitone blood-concentration variations are slight, and it remains to be proven that they are of clinical importance

If the missing control experiment were carried out it might be possible to show how worth-while economies could be made in the country's drug bill

Department of Pharmacology,
School of Medicine,
University of North Carolina,
Chapel Hill, North Carolina
John W Pearson

MITRAL VALVOTOMY AND PREGNANCY

Sir,—In his comments on our paper of March 15, Dr Richard Turner (April 5) states that "surgery during pregnancy is undesirable unless the evidence for tight [mitral] stenosis is based on severity of symptoms before pregnancy began" We think this goes too far, for we believe that Dr Turner underestimates the risk to life when a patient with mitral stenosis develops severe symptoms for the first time *during* pregnancy Although we agree that pregnancy may magnify the symptoms of mitral stenosis, we believe that valvotomy should be undertaken in at least some of these cases because

1 The risk of valvotomy during pregnancy is relatively reasonable (2 deaths in 97 cases)

2 The mortality is very high if pulmonary œdema develops during pregnancy (about 40%, unpublished data) and death does not usually occur in the first attack

3 When pulmonary œdema has occurred in pregnancy, a further pregnancy is too dangerous unless valvotomy is undertaken

Valvotomy (like termination of pregnancy) should not be undertaken until the cardiac condition has been adequately treated medically

We are surprised that Dr Turner demands "objective signs of long-standing pulmonary hypertension" and "an electrocardiographic pattern of right ventricular hypertrophy" before advising surgery In our experience such evidence is present in only about a third of patients with tight mitral stenosis, and the majority of these patients are so incapacitated that pregnancy is uncommon

E G Wade
W F Nicholson
Department of Cardiology,
The Royal Infirmary, Manchester
A Morgan Jones

TESTING OF STERILISATION METHODS

Sir,—Much misgiving has arisen on the value of testing sterilisation procedures by the use of heat-resistant spores It is quite easy to isolate from soil and dust aerobic-sporing bacilli which are able to stand up to a great deal of heat, but in our experience the spores rapidly lose this property on subculture For instance, an aerobic-sporing bacillus isolated from soil resisted being heated in a boiling-water bath for $1^1/_2$ hours, but a subculture of the same organism was destroyed in less than 2 minutes in the same water bath

The "test spores" issued by the Southern Group Laboratory until recently are killed in 7 minutes at 100°C Preliminary work by one of us (E H B) has shown that the survival power of spores is dependent on the method of preparing them, and in particular on their water content. Cultures incorporated in linen discs and then freeze-dried are much more resistant to heat than those dried by evaporation in warm air The freeze-dried preparations have been tested by placing a disc in a capped $^1/_2$ oz MacCartney bottle and not in an envelope This produces as closely as possible a "standard" preparation in a "standard" air-pocket, and under these conditions the discs have proved satisfactory

Conditions	Maximum internal temperature	*Bacillus subtilis* freeze dried	*B subtilis* evaporated	Browne's tubes yellow	Browne's tubes black	Browne's tubes green
Steam 30 min at 109°C or 5 lb per sq in	110 C	Not killed	Killed	Amber	Amber	
Steam 15 min at 115 C or 10 lb per sq in.	115 C	Killed	Killed	Green	Nearly green	
Steam 20 min. at 115 C or 10 lb per sq in.	116°C	Killed	Killed	Green	Green	
Hot air 60 min. at 160 C	160 C	Killed	Killed			Green

Because of the difficulty of obtaining, and maintaining, a "standard" test strain some pathologists have been relying on Browne's tube, which are supplied in the following forms

For glove sterilisation	yellow spot
For dressing sterilisation	black spot
For hot-air sterilisation	green spot

According to Medical Research Council memorandum no 15 (1955), gloves are satisfactorily sterilised at 109 C or 5 lb per sq in pressure for 30–40 min Unfortunately, the indicator in Browne's glove tube (yellow spot) will not satisfy these requirements, in that the colour change is often not amber, and certainly not green Heating to 115°C or 10 lb per sq in pressure for 15 min satisfactorily converts the red colour to green This treatment does not damage rubber gloves, and their normal life will not be diminished by this repeated steam treatment [1]

From the accompanying table it can be seen that freeze-dried spores resist 109°C or 5 lb per sq in pressure for 30 min., but are killed at 115°C or 10 lb per sq in pressure for 15 min, whereas the evaporated spores are killed in both cases

We cannot, therefore, rely on the present "sterility test packets" Freeze-dried discs will in future be issued for pathologists to transfer into MacCartney bottles

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[1] Butler, T C., Mahaffee, C, Wadell, W J *J Pharmacol* 1954 111, 425

[1] Howie, J *Lancet*, 1956, ii, 670

If double testing is not deemed necessary, the Browne's tubes can be taken as reliable This confirms the conclusions of Alder and Gillespie[2]

Group 9 Laboratory,
Watford, Herts
Southern Group Laboratory,
London, S E 13

HERTA SCHWABACHER
A J SALSBURY
E H BAILEY

ARTIFICIAL RESPIRATION WITH THE TUNNICLIFFE BREATHING-JACKET

SIR,—I read with great interest Dr Spalding's and Dr Opie's thorough report (March 22) on the Tunnicliffe breathing-jacket. In principle the jacket has seemed an advance on the cuirasse, as they have pointed out However, since it is more complicated to fit on the patient than the cuirasse, we have only tried it for respiration of three patients who were expected to need more ventilation than the Monaghan or ' Spirashell ' cuirasse would provide On these patients its performance has not come up to expectations

For the first of these, a boy aged 6 years, the smaller size of jacket proved too bulky On the second, a man with a collapsed left lower lobe and with a vital capacity of 50 c cm , it would only produce a tidal air of 190 c cm with a pressure of —27 cm of water Its performance on the third patient, a woman with a collapsed left lower lobe and a vital capacity of 90 c cm , was studied more fully, and the following figures were obtained (the tidal air was measured on a special small-volume-recording spirometer).

	Positive-pressure machine	*Tunnicliffe jacket*		*Spirashell cuirasse*	
Pressure (cm water)	+15	—27	—17	—27	—17
Tidal air (c cm)	410	350	220	350	250

A small or larger jacket produced lower figures

Although the Tunnicliffe jacket provided no better ventilation than the spirashell cuirasse, it was preferred by this patient because it was more comfortable, though it restricted arm movements

These two adult patients were more difficult to ventilate than usual This was shown by the relatively high pressure needed for correct ventilation by the positive-pressure machine In such cases we expected that the Tunnicliffe jacket might prove invaluable The figures above show that this was not so

Ham Green Hospital,
Pill, nr Bristol

R V WALLEY

LUNG RESECTION FOR BRONCHIECTASIS

SIR,—I agree with Mr Shaw (April 5) that your annotation of March 22 gives an unjustifiably gloomy picture of the modern results of resection for bronchiectasis Surely it is wrong to quote one small series alone as confirmation of the view you had stated previously, when the results of this series, for one reason or another, appear to be greatly inferior to those published by the many other workers in recent years Certainly lobectomy would seldom be justified if the risks were as great as you suggest, but in fact the operative mortality is probably considerably less than 1% in the best hands

New bronchiectasis developed in a third of the patients This is a very high proportion, but the statement means little unless one knows the degree and type of bronchial dilatation, and the severity of the associated infection and symptoms as compared with those present before operation

It is generally agreed that resection is often followed by some loss of lung function on the same side, but Long et al[3] showed that this may be compensated for by an increase in function of the other lung and that there may in fact be an increase in the maximum breathing capacity The mechanical and anatomical changes following resection may be harmful, but possibly not more so than the continued presence of a reservoir of infection with its tendency to local and occasionally distal spread

The indications for or against surgery in a particular case are sometimes clear cut, but in many a decision is difficult, not because the results of surgery are bad but because *the results* of both surgery and medical treatment are good

One of the reasons why it is so difficult to make broad generalisations about the relative merits of the two methods of treatment is that there are few if any published results of long-term medical treatment which can be compared fairly with the many surgical reports

I suggest, Sir, that an open mind should be kept on this difficult subject and that there is no good evidence on which to condemn resection for bronchiectasis

Chest Clinic,
The Marsden Hospital, Burnley

W H HELM

ADRENOCORTICAL STEROIDS IN MALIGNANT EXOPHTHALMOS

SIR,—We wish to support the plea by Dr Hoffenberg and Dr Jackson (March 29) for a further therapeutic trial of adrenocortical steroids in malignant exophthalmos We are prompted to report our experience with a recent patient

In May, 1956, a woman, aged 23, had a subtotal thyroidectomy For the previous seven years she had been increasingly nervous, had noticed excessive perspiration, and had lost 7 lb in weight In spite of these symptoms, she preferred hot weather Following the operation, the nervousness was only slightly improved, and she failed to gain weight

Slight protrusion of the right eye was first noticed four months before her operation, but later this became more severe, and in October, 1956, a right tarsorrhaphy was performed Her condition then remained unchanged until November, 1957 She then developed severe continuous frontal headache and pain behind both eyes The protrusion of the right eye became much more severe, and the left eye also began to protrude There was a rapid deterioration in vision in both eyes, especially in the right eye

On admission to the National Hospital on Nov 21, she had bilateral exophthalmos, more on the right, but no chemosis or conjunctival œdema Her visual acuity was reduced to counting fingers in the right eye, and to Jaeger (J) 20 in the left The visual field was full on the left, but the lower half of the right visual field was lost The right pupil did not react directly to light Bilateral early papillœdema was present There was severe restriction of bilateral upward gaze, and of abduction of the right eye Although she was nervous, there were no signs of thyrotoxicosis

She was treated immediately with prednisolone 10 mg t d s and triiodothyronine 10 μg t d s Because of the lack of improvement, a right orbital decompression was performed on Nov 23 This unfortunately failed to save the vision of the right eye, which became totally blind The left eye, however, dramatically improved, and by Dec 2 her visual acuity had increased from J20 to J2, the papillœdema had subsided, and her external ocular movements were full Thyroid gr ½ b d was substituted for the triiodothyronine, and she was discharged on this drug and on prednisolone 10 mg t d s

As an outpatient, she continued to take thyroid gr ½ *b d* but the dosage of prednisolone was progressively reduced to 5 mg daily over a period of one month The drug was completely withdrawn on Feb 26 Five days later, she developed mistiness of vision of the left eye, and two days later this became much more severe She was readmitted on March 5 There had been a considerable increase in the degree of proptosis of the left eye, and her visual acuity was reduced to J10 There was complete loss of the temporal half-field, and the defect also spread to involve most of the lower nasal quadrant The external ocular movements were full, and the left disc was

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2 Alder, V E , Gillespie, W A *J clin Path* 1957, 10, 299

3 Long J H , Norris, C M , Burnett, W E , Wester, M R *J thorac Surg* 1950, 19, 477

normal The right eye was blind, with optic atrophy and a fixed dilated pupil

She was immediately started on prednisone 20 mg t d s, and within thirty-six hours there was much improvement The visual field defect began to shrink, and the visual acuity increased By March 11, her visual acuity had become normal (J1), and only a minimal peripheral temporal field defect remained This defect has since disappeared She has continued to take thyroid gr $^{1}/_{2}$ b d, but the dosage of prednisone has now been reduced to 10 mg t d s

This case has proved instructive Although decompression failed to save the sight of the right eye, the left eye improved after operation and this may have been due to the prednisolone which was being concurrently given The relapse of the left eye followed five days after stopping prednisolone, and impressive improvement began within thirty-six hours of resuming steroid treatment Although no firm conclusions can be drawn from a single case, we feel that it is reasonable to attribute this patient's improvement to steroids, at any rate we do not propose to risk withdrawing treatment a second time

We wish to thank Dr Denis Brinton for permission to report this case

The National Hospital for Nervous Diseases,
London, W C 1

R W HORNABROOK
J C LEONARD

PRE-ECLAMPTIC TOXÆMIA

SIR,—Dr Margaret Robinson (Jan 25) holds that the ingestion of extra sodium chloride in the diet is successful in the prevention of toxæmia of pregnancy, but I believe that her study has many shortcomings Because of the large circulation which *The Lancet* has to the medical profession of this country, I think that this article is more damaging to prospective mothers and to the information of those concerned with their care than any other piece of literature presented to the obstetrician in the past thirty years

We have statistically analysed Dr Robinson's data We found that they were statistically significant in the overall groups In the age-groups 0–30 and 30–50, the data were significant where toxæmia was commoner among those on salt-poor diets The data were significant as regards parity only up to para 4 but were not significant beyond this parity The neonatal deaths and the presence of œdema showed statistical significance On the other hand, there was no statistically significant correlation among the prenatal deaths, antenatal bleeding, and antepartum hæmorrhage We could not differentiate between antenatal bleeding and antepartum hæmorrhage

Although statistically significant differences existed between the low-salt and the high-salt group, this does not necessarily mean that the patient was protected against toxæmia because of the high-salt diet just because 70% of the patients on the high-salt diet did not develop a toxæmia according to the definition given in the paper Some other comparisons might be drawn relative to toxæmia of pregnancy too

Chesley (personal communication) has shown that there is a statistically significant correlation between the presence of toxæmia of pregnancy and membership of the Baptist Church We have been able to show a high incidence of toxæmia of pregnancy in underweight patients—but also in those who are overweight It thus seems that some other variable existed as a third factor in the group of patients reported by Dr Robinson In England, where there still exist difficulties in getting satisfactory nutrients, why could not the variable of nutrition account for the differences noted in her series? Also, it is not known whether her patients on the increased salt intake were not in various degrees of salt depletion before the administration of supplemental sodium chloride It seems as though there was no actual control over the sodium-chloride intake among these patients, they were merely instructed to increase their salt intake It might be open to some question whether the patients actually complied with the advice offered, and even if they did comply by increasing their intake, they may conceivably have increased it only to a level that would be reached by another group who reduced their sodium-chloride intake

Even under the strictest metabolic conditions of study in hospital patients, there are difficulties in controlling compliance with rigid regimes The study was not controlled in a hospital, nor were there any biochemical, weight, or endocrinological investigations

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RUSSELL R DE ALVAREZ

CARDIAC SYNCOPE AFTER SWALLOWING

SIR,—Concerning Dr James' interesting paper last week, may I just mention, for the sake of completeness, a case of a similar syndrome which was published by myself and H Uiberall[1]

A lady, aged 62, had a characteristic Stokes-Adams syndrome with unconsciousness, after swallowing food or fluids first thing in the morning The electrocardiogram showed signs of sinus bradycardia and ventricular extrasystoles During the attack, the pulse-rate dropped from about 80 to 44 and the blood-pressure from 220/100 to below 80/0 mm Hg The attacks began soon after a bout of tonsillitis At the time of the hospital investigation it was possible to produce an attack by touching the left posterior arch of the soft palate After a severe attack there was a refractory phase for over an hour which could be used for the intake of large amounts of food without provoking further attacks The left tonsillar region was anæsthetised and radium 100 mg implanted for 3 hours The attacks increased in intensity for the next 2 or 3 days On the 7th day a second application of radium was carried out with renewed intensity of attacks lasting about 7 days From the 8th day onwards after a second insertion of radium the attacks disappeared, and the patient remained free from attacks for the next $9^{1}/_{2}$ months

London, S W 1

V C MEDVEI

INDIRECT BILIRUBINÆMIA

SIR,—The observation by Danoff et al (*Science*, April 4, *Lancet*, Feb 8, p 316) that glucuronic acid and its sodium salt administered to infants with hyperbilirubinæmia resulted in a striking but transient fall in unconjugated bilirubin is of extreme interest to all pædiatricians In our work with glucuronic acid we have been unable as yet to demonstrate a significant fall in bilirubin level However, we wish to call attention to the potential hazard in the use of these preparations in view of the fact that physicians may be tempted to substitute glucuronic-acid therapy for replacement transfusions in newborns with dangerously high serum-bilirubin levels Should the reported findings be confirmed, there is no indication regarding the fate of the declining serum-bilirubin The possibility has not been excluded that bilirubin is driven from the blood into the tissues, thus increasing the risk of brain damage

Until further investigative work determines the exact pharmacodynamic action of these compounds we feel strongly that physicians should refrain from using them in the newborn

Boston City Hospital,
Boston 18, Massachusetts, U S.A.

RUDI SCHMID
GLORIA JELIU
SYDNEY S GELLIS

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[1] Medvei, V C., Uiberall, H *Wien klin Wschr*, 1938, 51, 234

THE DOCTOR'S ATTITUDE TO HIS PATIENT

SIR,—Because Dr Ryle (April 12) is the fortunate possessor of such characteristics that he can adequately treat his patients he should not decry the endeavours of us others to understand our patients better, or deny that we others do need to suffer a change before that can happen

I am sure "we" are in the majority otherwise, would there be so many "doctor satellites" revolving, as hopelessly as "Laika", around our surgeries?

We all suffer a "sea-change" in the depths of our personalities by constant contact with those around us, but the change into something richer and more understanding is quicker in the greater awareness of a seminar such as Dr Michael Balint's

Dr Ryle and Dr Tuckman (March 29) have evidently had no such experience For my own I shall always be grateful

Ilford, Essex R N COMPTON SMITH

A SLIDE-HOLDER FOR STANDARD FILING CABINETS

SIR,—The problem of storing a large number of lantern slides or dental radiographs compactly and yet in a way which makes them readily available for inspection and selection may be solved by the construction of slide-holders in the following way

Strips of transparent polyvinyl chloride (P V C) ($1^3/_4$ in × $14^1/_2$ in) are welded on to a sheet of natural P V C ($10^1/_2$ in × $14^1/_2$ in) to form twenty-four pockets, each holding one 2 in × 2 in slide (fig 1) Welding is by radio frequency

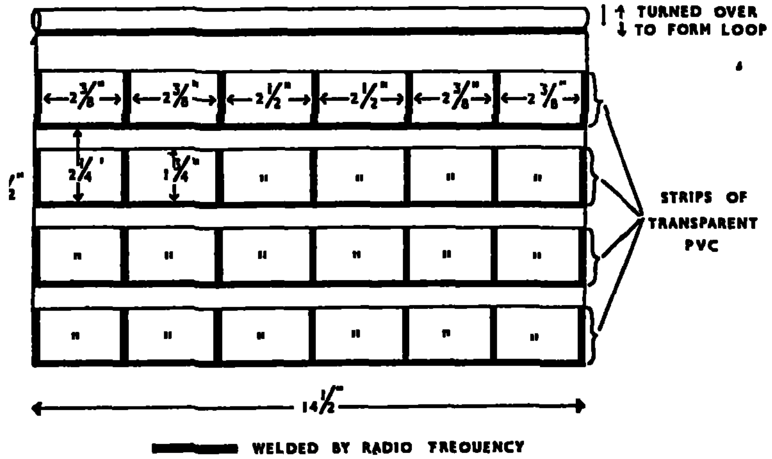

Fig 1—Dimensions of slide-holder

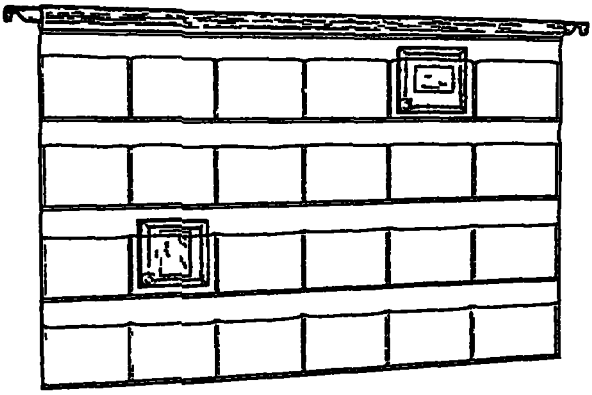

Fig 2—Slide-holder complete

At the top of the frame a loop is made to hold a standard filing-cabinet metal bar (fig 2) The frame can then be placed in a filing-cabinet drawer, each drawer holding about 100 frames, or 2400 slides For catalogue marking or indexing a typed card can be slid in the loop holding the metal bar, typescript can be seen through the translucent P V C

All the slides in a frame may be viewed by holding the frame up to window light (the P V C diffuses the light giving a standard illumination), or by hanging in front of a standard X ray viewing-box

For transport of slides the metal at the top of frame can be withdrawn, the whole plastic framework can then be folded into a neat package and carried in the pocket The materials to make one such holder cost about 1*s* 6*d*

Holders can be made similarly to take $3^1/_4$ in × $3^1/_4$ in slides, dental radiographs, or photographic transparencies For demonstration purposes larger holders can be made to cover the whole of a viewing-box screen

Sheets of P V C were supplied by Commercial Plastics, and strips ('Vybak') by Bakelite Ltd

Department of Surgery,
University of Durham J E ROGERS

BLEEDING ULCER IN A MECKEL'S DIVERTICULUM

SIR,—Complications arise in 11% of cases of Meckel's diverticulum—intestinal obstruction, diverticulitis, and peptic ulceration with hæmorrhage or perforation

Lecène[1] says that peptic ulcers of Meckel's diverticulum are constantly to be found where the mucosa of the small intestine meets an islet of ectopic gastric mucosa—usually at the base of the diverticulum This leads to the accepted hypothesis that the peptic activity of this ectopic mucosa produces autodigestion and ulceration of the intestinal mucosa This concept allows a distinction between ulcers due to inflammation and those due to mechanical causes such as intussusception of the diverticulum

Intestinal bleeding from these ulcers is usually slight, but sometimes it may be severe, appearing in the stool as red blood and recent clots, and endangering the patient's life

A boy, aged 2 years, had been in hospital three times in 1955, for whooping-cough, gastrointestinal disorders with generalised urticaria, and an unidentified fever He had passed some ascarids in the stool On Nov 23, 1956, he suddenly became intensely pale, giddy, and cold His temperature went up to 102 8°F (39 3°C) and next morning he passed a stool almost entirely composed of fresh blood, about 600 ml At 3 P M we noted intense pallor of mucous membranes and skin (pulse 140 a minute, blood-pressure 80/60 mm Hg) There was peri umbilical tenderness, and the abdomen was slightly distended, with transient and local muscular guarding below the umbilicus No mass could be felt or seen in the rectum, but the exploring finger was stained by fresh blood An abdominal radiograph showed gas in the intestines without fluid levels Hæmoglobin 57%, red cells 2 72 million per c mm, clotting-time 8 min, bleeding-time 3 min

The presumptive diagnosis was bleeding from an ulcer in a diverticulum, and operation was undertaken on Nov 24 300 ml of whole blood was transfused during the operation and another 300 ml postoperatively The small bowel was slightly congested and distended by gas The large bowel was dark purple and full of blood About 30 cm from the ileocæcal junction was a Meckel's diverticulum on the antimesenteric border Its tip was congested and contained a tumour the size of a lentil Very many ascarids could be felt in the small ntestine The diverticulum was removed and its stump nvaginated without narrowing the lumen of the ileum

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[1] Lecène, cited by Forgue, E. *Précis de pathologie externe*, vol II, p 676 Paris, 1939

The postoperative course was complicated by persistent paralytic ileus, with abdominal distension and vomiting, which subsided only after continuous gastric suction for 48 hours An enema returned black blood and clots in great quantity Intravenous fluids were given On Nov 26 the Hb was 72%, and 600 ml blood was transfused On the third postoperative day the child was allowed out of bed, and on Dec. 5 he was discharged

The diverticulum was 4 cm long, and 1 3 cm wide at the base The mucosa was generally of the small-intestine type, but at the tip of the diverticulum was an islet of gastric mucosa Just near this was an ulcer, smaller than the ectopic tissue, not very deep, covered with a clot of blood Microscopic examination of the specimen (Dr H Breazu, Ploesti) showed at this level a deep layer of tubular glands of gastric type

The diagnosis was difficult in that the patient had had no previous alimentary-tract hæmorrhages, the illness started with fever, X-ray examination was inconclusive, and there was no umbilical anomaly to point to a diverticulum

The ulcer is usually situated near the point where the mucosa of the ileum joins that of the diverticulum, but in this case this region was normal An ulcer at the tip of the diverticulum is very rare, and we have found only one report of such a case [2]

When one of these ulcers bleeds, operation is always necessary, for death may be caused by continued hæmorrhage into the gut, perforation followed by generalised peritonitis, or ulceration of the mesodiverticulum with intraperitoneal hæmorrhage [3]

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Rumania

CONSTANTIN CEPLEANU
ION TUTICA

HOOKWORM AND ANÆMIA

SIR,—The association between hookworm infestation and iron-deficiency anæmia is almost traditional Bilharz first described hookworm in Egypt in 1851 Three years later his pupil Griesinger [4] linked hookworm infestation with the disease called Egyptian chlorosis Ashford's [5] description (1900) of patients in Puerto Rico with severe anæmia and heavy infestation with the worms received wide recognition Thereafter ancylostomiasis was regularly added to the list of causes of iron deficiency in standard textbooks of medicine

Loss of blood at the site of attachment of the worms was generally thought to be the immediate cause of the anæmia But in recent years some serious doubts have been expressed The load of worms, as judged by the ova count in the fæces, rarely correlates with the severity of the anæmia Furthermore patients with an apparently heavy infestation are not always anæmic The suspicion has grown that the association between hookworm and anæmia is fortuitous, since people infested with the worm commonly live on diets composed chiefly of cereals, poor in proteins, calcium, and ascorbic acid On such a diet defective absorption of iron would be expected Foy and Kondi [6]—two hæmatologists with wide experience in the tropics—have summarised present views as follows "The consensus of opinion then is that hookworms are not a common càuse of anæmia, but until more critical work has been done it is better to leave the question open "

At this moment of uncertainty we wish to draw attention to the original observations of Boycott and Haldane,[7] who investigated the cause of severe anæmia among tin-miners in Cornwall This had been attributed to bad air, but this explanation they quickly put out of court Boycott and Haldane found that the men were heavily infested with *Ancylostoma duodenale*, the larvæ of which penetrated their clothing soaked in mine water Some of the men had less than 40% of hæmoglobin Such a degree of anæmia in an adult male could not possibly be attributed to any defect in the common British diet of that time

Boycott and Haldane added a remarkable observation Using the carbon-monoxide method for measuring blood-volume, developed in Edinburgh by Haldane and Lorrain Smith,[8] they showed that in some of the anæmic Cornish miners the blood-volume was increased, so that the anæmia was due to hæmodilution rather than to loss of blood from the gastrointestinal tract

We suggest that a properly financed research project into the association between hookworm and anæmia is now overdue

Departments of Medicine and Physiology,
University of Edinburgh.

A P MEIKLEJOHN
R PASSMORE

ESSENTIAL FATTY ACIDS, LIPID METABOLISM, AND ATHEROSCLEROSIS

SIR,—In *The Lancet* of April 5 Dr Keys takes exception to statements contained in our paper which appeared on Feb 15 If we have misquoted Dr Keys, we are very sorry indeed I should, however, like to point out that, in the field of dietary fats, it is very difficult *not* to misquote Dr Keys, inasmuch as his concepts and statements have differed very radically from one year to the next Perhaps this is to some degree unavoidable in a field in which knowledge is progressing very rapidly We should, however, like to suggest that the presentation of precise mathematical formulations that enable one to predict precisely that John Smith's cholesterol level will be precisely so much, in response to precisely so much saturated and unsaturated fat, is very premature indeed As noted in our paper of Feb 15, not only the relative but the absolute amount of polyunsaturated fat required to produce a given fall in the level of cholesterol and other plasma-lipids varies markedly with the age of the patient, and the presence of known atherosclerosis Older individuals with obvious vascular disease may for a time require complete removal of saturated fat from the diet and the administration of large amounts of linoleic-acid-containing fat, in order to obtain a significant and maintained fall in lipids Young normal individuals may respond to quite modest amounts of polyunsaturated fats in the presence of appreciable amounts of saturated fat

We can agree in part with Dr Keys' present thoughts —that is, those of his thoughts stated in his letter in the April 5 issue of *The Lancet*—regarding the relatively "neutral" properties of oleic acid as compared to carbohydrate, if one considers only the effects upon plasma-cholesterol levels However, the effects upon plasma-triglyceride are very different, inasmuch as, at least in our experience, there is a very marked rise in plasma-triglyceride when carbohydrate is substituted for any type of fat in the diet. This is not observed when highly purified ethyl oleate is administered Conceivably, the

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2 Moore, C T *Surg Gynec. Obstet* 1956, 103, 569
3 Weese, K. *Zbl Chir* 1954 79, 588
4 Griesinger, W *Arch physiol Heilkunde*, 1854 13, 555
5 Ashford, B K. *N Y med J* 1900 71, 552.
6 Foy, H , Kondi, A *J trop Med (Hyg)* 1957, 60, 105

7 Boycott, A E., Haldane, J S *J Hyg , Camb* 1903, 3, 95
8 Haldane, J S , Lorrain Smith, J *J Physiol* 1900, 25, 33

elevated triglyceride level with high carbohydrate feeding is in some way related to marked acceleration of lipogenesis

A final comment concerning "essential-fatty-acid deficiency" an essential nutrient, by definition, is one which cannot be synthesised in the body in adequate amount If it is not supplied in the diet, its absence will eventually be associated with abnormalities of structure and/or function Linoleic acid appears to fulfil the requirements of this definition The fact that, in abnormal individuals, relatively large quantities are required to produce the desired metabolic effects seems to us beside the point, insofar as "essentiality" is concerned When we have a solid understanding of the way in which linoleic acid lowers plasma-lipid levels, we will be in a much better position to talk of physiologic *versus* pharmacologic effects

Institute for Metabolic Research,
Highland Alameda County Hospital,
Oakland, California

LAURANCE W KINSELL

ABSENCE FROM WORK ON A MEDICAL CERTIFICATE

SIR,—Dr Ashworth (April 5) must be given the benefit of the doubt in case he is really trailing his coat However, he reports the case of the father of two sick children whose wife is working in fear of dismissal, in which it seems indefensible to issue a National Insurance medical certificate

Humanity should be satisfied, by all means, by giving a note for the respective employer of father or mother stating that their children are ill and require the attention of a parent, but to confuse humanity with "expeditiousness" seems wrong

To advocate this wide interpretation of sickness certification, whilst expedient, will in fact discredit the National Health Service further (or rather the general practitioner) and substantiate the employers' mistrust of medical certificates Such interpretation will encourage all the other parents, who as yet are too self-respecting, to follow this example at the next opportunity

Sickness benefit for a parent is not to be confused with payment for parental duties The statement which the doctor signs on form Med 1 is that his patient is incapable of work

The specious argument—that 5% or 3% of £840 million is a negligible sum, which can be ignored and is cheap at the price for wrongful application of sickness benefits—holds no water There are many necessary improvements in the Health Service which could be carried out if this sum were available

Edinburgh

E V KUENSSBERG

SIR,—Many of us will have been given food for thought by Dr Ashworth's excellent article One is relieved to see the relative smallness of unjust claims, and this is probably easily offset by those who work when, by all the rules, they should be in bed (though most of us could say from experience that this has surprisingly few ill-effects)

Unless there is clear evidence to the contrary, one has to accept that the patient is giving the facts as he knows them To start on the assumption that one is being misled, as I suppose a professional referee has to do, would make life impossible, and, anyway, in self-defence one has to play for safety A patient who collapses with pneumonia or coronary disease after being sent off to work lends no credit to the profession, nor is the man who has to be sent home with a temperature after seeing his doctor on the way to work when his temperature was normal As Dr Ashworth says, one may have to observe a patient for a time before making a firm decision

Arising from this I should like to raise another issue It seems to me impossible to give an honest note in a large proportion of requests for a day or two's absence If pressed, one could write a full report in which the pros and cons could be stated, and for which the proper fee would be charged While giving what is in effect a duplicate of a "panel" note for, say, 2*s*, is a reasonable proposition and a convenience to employer and employee, to certify for 2*s* that a man is unfit to work today but will be recovered from his lumbago tomorrow is a convenience only to the dishonest By this means a man can blackmail his employer—who may well know that he was at a football match—into paying him a bonus This policy has brought certification into contempt both by employer and employee, as I well know from speaking to both "Anyone", they say, "can get time off if they pay their doctor 2*s*"

I believe that employers would get less absenteeism if they relied upon a written statement from the worker—the majority of whom are honest—and it would save the genuine patient the inconvenience of waiting in the surgery It would save the drug-bill the cost of innumerable bottles of medicine which one feels bound to give to relieve symptoms in patients one has decided are not fit for work, and I am sure it would improve the status of doctors if they did not show themselves so ready to be deceived I know that this has been debated more than once by the B M A, but on the grounds I have given I would appeal for a discontinuation of the practice of what is in effect, though not intent, misleading certification

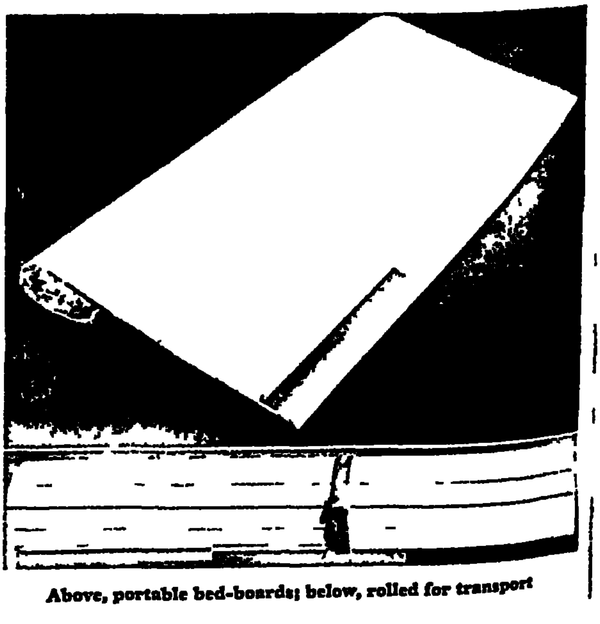
Shirley, Solihull,
Warwickshire

W BRIAN GOUGH

PORTABLE BED-BOARDS

SIR,—Thousands of people with backache, due to intervertebral-disc and other lesions, now prefer to sleep on hard beds These people must avoid the well-sprung mattress Holidays and visits away from home are spoiled by backache through sleeping in comfort

I have had made for me what might be described as a small tap-mat—made of hard wood and backed with canvas This can be rolled up, put in a car, and carried round with ease—then laid under a mattress When rolled



Above, portable bed-boards; below, rolled for transport it measures only 6 in in diameter It has proved a great success

It was made for me by Messrs Capes, of Sutton Lane, London W 4 Mr Cape too has backache, so he took a special interest and now has one for himself

London, S W 7

O S THOMPSON

MODIFIED TRACHEOTOMY TUBE

SIR,—I was most interested to read Dr Napier's letter of April 5

Unfortunately he did not illustrate his tube,[1] which he described as "a skeleton tube with open back" It would seem that its main purpose was to facilitate the "weaning" of the child back to normal breathing

I feel that Dr Napier has perhaps not fully appreciated the reason for the modifications I describe (March 15) There are in fact several modifications, all equally essential to enable it to perform its function The tube is designed to facilitate coughing in the acute stages of respiratory infection, such as tracheobronchitis and bronchopneumonia or in chest injuries It also allows for inflation of the lungs following suction, the use of controlled ventilation should it be required, and the induction of anæsthesia if bronchscopy is necessary

Alder Hey Children s Hospital,
West Derby, Liverpool

FRANK WILSON

LONG-TERM ANTICOAGULANT TREATMENT FOR CORONARY-ARTERY DISEASE

SIR,—In Dr Hougie's letter last week I am sure a misprint has occurred "There is no evidence that there is present in normal plasma a factor which can restore the prolonged bleeding-time of patients with von Willebrand's disease to normal" should surely read "There *is* evidence " Most probably Dr Hougie is referring to the factor already described by Nilsson et al.[2]

Southern Group Laboratory,
Hither Green Hospital,
London, S.E.13

P WOLF

*** We are grateful to Dr Wolf for drawing attention to our mistake in reproducing Dr Hougie's "There is *now* evidence " as "There is *no* evidence "—ED L

PENICILLAMINE AND DIMERCAPROL

SIR,—In his article entitled Penicillamine, a New Oral Therapy for Wilson's Disease, Dr J M Walshe[3] writes

> "A new form of oral treatment with dimethyl cysteine (penicillamine) is described. Given in doses varying from 0 5 to 1 5gm. daily to six patients with Wilson s disease, it provoked a very large increase in the urine excretion of copper, in five patients it proved more active than BAL in this respect."

Citing Dr Walshe's article, the statement is often made (e g, by Dr Boulding and Mr Baker[4]), that penicillamine "appears to be more efficacious than dimercaprol"

If two drugs are to be quantitatively compared, equimolar amounts should be given using the same vehicle and the same route of administration, but in Dr Walshe's studies the penicillamine was given orally by capsule while dimercaprol was administered intramuscularly and probably dissolved in oil

In a forthcoming article[5] dealing with the ability of penicillamine to protect rats against the lethal effects of mercuric chloride, I present evidence indicating that when equimolar amounts of dimercaprol, *dl*-penicillamine, or *d*-penicillamine dissolved in saline are tested intramuscularly, dimercaprol is definitely superior to *dl*-penicillamine and only slightly superior to *d*-penicillamine under the conditions of our experiments It would be of interest to compare equimolar amounts of penicillamine and dimercaprol, administered by the same route and in the same vehicle, to determine the relative activities of these drugs on the excretion of copper

Department of Pharmacology,
School of Medicine, Vanderbilt
University, Nashville, Tennessee.

H VASKEN APOSHIAN

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[1] Napier, W *Lancet*, 1937, ii, 673
[2] Nilsson I M, Blombäck, M, Jorpes, E., Blombäck, B, Johansson, S A. *Acta med scand* 1957 159 179
[3] Walshe, J M. *Amer J Med.* 1956, 21, 487
[4] Boulding, J E, Baker R. A. *Lancet* 1957, ii, 985
[5] Aposhian, H V *Science* (in the press)

Public Health

More Radioactivity in Britain

Kodak Ltd make daily measurements of London radioactivity to safeguard their photographic manufacturing processes, and they detected an increase in late March[1] The activity reached a peak on March 24, when it was 10–20 times normal (it was 100 times the normal after the Windscale accident) The Atomic Energy Authority[2] has since confirmed that there was a "small but sharp" temporary increase in radioactivity over Britain during the second half of March It is assumed that the increase was due to the recent series of bomb tests in the Soviet Union, and was caused mainly by short-lived fission products The Authority is to keep a careful watch in the coming months for the longer-lived and more dangerous products

Tuberculosis and Cancer in 1957

IN England and Wales last year the death-rate from tuberculosis and the maternal mortality-rate both reached new low records There were 4250 deaths from respiratory and 534 from other tuberculosis, giving rates per million of 95 and 12 respectively Since 1947 the death-rate from respiratory tuberculosis has fallen by 79% The maternal mortality-rate per 1000 live and still births was 0 47 (0 39 excluding abortions) There were 349 deaths from maternal causes (excluding abortion) compared with 399 the year before These are provisional figures[3]

The death-rates from cancer were 2312 per million for men and 1891 for women, the figures for 1956 were 2274 and 1891 About 33% of the male and 6% of the female cancer deaths were from lung cancer, and the death-rates from this disease increased from 726 per million in 1956 to 759 for men, and from 111 to 116 for women.

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[1] *Times*, April 5
[2] *Scotsman*, April 10
[3] Registrar General s Weekly Return for England and Wales, no 14 H.M Stationery Office Pp 20 1s 6*d*

Infectious Diseases in England and Wales

Disease	Week ended March				
	1	8	15	22	29
Diphtheria	3	1	1	2	2
Dysentery	1333	1068	1187	1173	1588
Encephalitis					
Infective	3	4	4	4	1
Postinfectious	2	1	1	6	
Food-poisoning	124	149	144	173	154
Measles, excluding rubella	4353	4532	4012	4631	4259
Meningococcal infection	25	24	29	20	22
Ophthalmia neonatorum	40	40	34	37	36
Paratyphoid fever	4	6	2	1	4
Pneumonia primary or influenzal	773	690	537	514	622
Poliomyelitis					
Paralytic	10	5	13	21	17
Non-paralytic	5	5	5	6	4
Puerperal pyrexia	226	199	207	205	232
Scarlet fever	797	938	910	965	996
Smallpox				1	
Tuberculosis					
Respiratory	574	591	586	486	545
Meninges and C.N.S.	11	11	6	9	9
Other	53	67	68	53	64
Typhoid fever	2		3	2	3
Whooping-cough	525	620	555	587	651

Obituary

JAMES DRUMMOND GRAHAM

Kt, C B, C I E, M B Glasg, D T M

Major-General Sir James Graham, formerly public-health commissioner with the Government of India, died on April 4 at the age of 83

Having been resident physician at the Glasgow Royal Infirmary, he entered the I M S in 1900, and saw military service in Waziristan Before the first world war, with an appointment in the United Provinces, he was doing valuable work on malaria, showing a decided aptitude for medical research he was one of a number of senior officers who, under a planned scheme, were making the first malaria survey of all India For the eight years 1915-23, however, he was away from India—first on the staff of the Egyptian and Mesopotamian expeditionary forces, and later, from 1920, as director-general and inspector-general of the Iraq health services and adviser to the Ministry of Public Health On his return he became public-health commissioner with the Government of India, and in 1932 he officiated for some months as director-general, I M S In his post as commissioner, writes S R C, "he excelled as an administrator Whilst public-health administration in India was the direct responsibility of Provincial Governments, overruling control of public health and medical research lay with the Central Government, and Sir James Graham played a vital part in development of public health and medical research organisation in India He was, moreover, no remote and inaccessible official He worked quietly and understandably in friendly consultation, always helpful and encouraging He was I think liked by everybody for his friendly simplicity and kindness There was something very straight and fresh about Graham and one was always stimulated by him As a Lowland Scot (he came from Ayrshire) he had a streak of canniness in his make-up, but this did not affect his giving ungrudging help and encouragement at all times to the schemes of others"

Internationally he was known to many as delegate for British India in the Office Internationale d'Hygiène Publique, a member for some years of the Health Committee of the League of Nations, and chairman of the advisory committee of the League's eastern health bureau at Singapore He was appointed C I E in 1919 and C B in 1931, and was knighted in 1934, the year of his retirement

J M writes of his "old and greatly valued friend" "His record of services shows that he was selected for a succession of important appointments demanding exceptional qualifications The many honours conferred on him testify to the conspicuous success with which he filled all these posts This was due not only to his great professional qualifications but also to his personality, which made him universally popular with his colleagues and others with whom he came into contact, irrespective of race or nationality It was by no means a case of his being 'hail fellow, well met!' but of his natural friendliness of disposition and his cosmopolitan outlook on life"

He married in 1912 a daughter of Colonel C Seymour, A M S, and they had one son In later life Sir James and Lady Graham lived for some years in a country house in the south of France Progressive failure of his eyesight made reading and writing difficult, but did not prevent his corresponding with his friends from Indian days

Births, Marriages, and Deaths

BIRTHS

HADDOCK—On March 20, in Tanganyika, to May, wife of David Haddock, M.R.C.P—a son, John Keith

Notes and News

A NATIONAL LIBRARY OF MEDICINE?

A MEMORANDUM prepared by the medical section of the Library Association expresses concern at the decision to omit clinical medicine from the coverage proposed for the National Lending Library for Science and Technology The need for a national library of medicine, the Association points out, has been felt for many years, for the two largest general medical libraries in this country—those of the Royal Society of Medicine and the British Medical Association—exist to serve their members and have had to reduce the help they used to give other libraries A national medical library service is needed particularly by the research-worker with non-medical qualifications

Individual medical schools, postgraduate institutions, and research organisations cannot hope to provide and house libraries sufficiently wide in scope to satisfy from their own resources all the potential needs of their users Inter-library lending has increasingly become an unsatisfactory answer to the problem of meeting those wide needs

Moreover the ever-increasing volume of "medical" literature, the increasing variety of forms of publication (to the monograph and journal must now be added the symposium, the research conference proceedings, the project report, the transcript of a tape-recording, and so on), and the diversity of sources from which *one form or other of publication comes, demand a correspondingly greater effort for their tracing* and acquisition The individual working library cannot provide that effort It is better that each should, whilst maintaining a search and acquisition service adequate for its regular needs, be able to turn to a central source

There appear to be two practicable solutions to the problem of providing a national service of medical literature

1 A National Library of Medicine could be built on an existing comprehensive medical library

2 The scope of the new National Lending Library of Science and Technology could be widened to include medicine in its broadest aspects

The Library Association recommends a thorough examination of the possibility of creating a National Library of Medicine based on the present collections of the Royal Society of Medicine, cooperating and discussing policy with the National Lending Library of Science, as at present envisaged, and making its services available on the same lines If this proves impossible, the Department of Scientific and Industrial Research should consider covering the whole field of medicine in its broadest aspects by the National Lending Library of Science and Technology

TUBERCULOSIS IN THAILAND

IN Thailand, which has some 18 million inhabitants, a tuberculosis service was established by the Thai Government late in 1949, and a central chest clinic—the first of its kind in the country—was set up in the heart of Bangkok In 1951 the World Health Organisation and UNICEF gave active assistance through the W H O tuberculosis control project, described in our columns by the late Dr Benatt[1] who became its director This project was limited to two years, but much of its work has been continued The central chest clinic has now become the tuberculosis demonstration and training centre, working in association with the tuberculosis hospital at Nonburi, about 15 kilometres from Bangkok It forms part of the division of tuberculosis control headed by Dr Prakorb Visalvet, and on the medical side Dr Nadda Sriyabhaya is the physician in charge

The average number of deaths attributed to pulmonary tuberculosis in Thailand is about 10,000 a year, giving a mortality-rate of about 60 per 100,000, but the number among the 900,000 inhabitants of Bangkok is 1500 (or about 200 per 100,000), and this suggests that outside the capital many cases go unrecognised because facilities for diagnosis are lacking The percentages of positive reactions obtained (with 5 T U of purified protein derivative) in rural areas (5,166,363 persons) and Bangkok (111,727 persons) are

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[1] Benatt, A J *Lancet*, 1956, i, 737

Age-group	*Rural*	*Bangkok*
1–6	16·6	32·9
7–14	40·4	68 1
15 and over	78·5	88·5
Total	51·9	71 9

On mass radiography of some 30,000 people in Bangkok and its neighbourhood during 1953–55 it was found that on miniature film about 5% of the population of Bangkok had an abnormality suggestive of tuberculosis About 1% were positive on bacteriological examination

Attendances at the central chest clinic increased from 1500 a month in 1952 to 8000 in 1956 The average number of new patients visiting the clinic is now 800 a month, of whom about 40% are found to have pulmonary tuberculosis In a month this laboratory handles about 700 direct smears of sputum and about 800 cultures

Since there is only one tuberculosis hospital, with a capacity of 200 beds, facilities for institutional treatment and isolation are still very limited As a routine, tuberculosis patients receive two of the three drugs (streptomycin, isoniazid, and P.A S), and cases are supervised at home by public-health nurses who give preventive instruction to patient and family In 1956 a lay visitor was also employed to do home visiting A refill clinic was also maintained as supplementary treatment, because very few patients were able to take long enough rest

A contact clinic is held daily to give B C G vaccination to the tuberculin-negative and to examine those with positive X-ray findings Of 6299 contacts X-rayed during 1953–56, 8% were found to have pulmonary tuberculosis and 1% were positive for tubercle bacilli As another preventive measure, young children and infants in contact with tuberculosis patients are referred to a central preventorium for children, where they are isolated until B C.G has given them a positive tuberculin reaction.

A social service was started last July, and cases referred by the public-health nurses are investigated by the social worker, who reports on their needs Previously the afflicted families could get some help from the public-welfare department or charitable organisations During 1956, 102 such families received economic support besides free medical service

The mass B C.G campaign was launched in March, 1953, and 6,652,964 people had been tested, and 2,330,743 negative reactors vaccinated, by the end of 1956 The mass campaign completed, vaccination is entering on a phase of consolidation as part of the permanent national health scheme that is, the use of vaccine is to be continued on (1) contacts of tuberculosis cases, (2) schoolchildren, and (3) persons at special risk

The tuberculosis hospital at Nonburi, the only one in Thailand, was incorporated in the tuberculin project in 1951 By the end of 1956 the number of beds had risen from 75 to 200 A thoracic surgical unit was set up in 1952, and major operations in 1952–56 numbered 234 Both the central chest clinic and the hospital have become training centres for student nurses, qualified nurses, medical students, and public-health personnel To relieve the shortage of nurses a school of nursing aides was started in 1956 The course lasts a year

BLOOD-TRANSFUSION

THE Ministry of Health, in association with the Department of Health for Scotland, is shortly issuing a revised edition of *Notes on Transfusion* This follows closely the lines of the previous one (1954), but certain additions give the text greater clarity There are also some minor but important alterations for example, peanut oil has now been omitted from the diet in the treatment of transfusion reaction, and sodium lactate now replaces sodium bicarbonate in the stage of oliguria. Section IX, on the rhesus factor, has been considerably expanded and much improved Consultants as well as their juniors will find this unassuming little book of 21 pages well worth reading

DIAMOND JUBILEE OF R.A.M.C

IN honour of the diamond jubilee of the Royal Army Medical Corps, a commemorative oration, by Sir Gordon Gordon-Taylor, entitled *In Arduis Fidelis*, will be delivered in the great hall of B M.A. House, Tavistock Square, London, W C 1, on Wednesday, June 25, at 5 P M The oration will be open to the public without ticket, but past and present members of the Corps, with their ladies, are especially invited

The British Medical Association played a considerable part in the events that led to the formation of the R A M C in 1898 For some years it had pressed for reform of the Army's medical organisation, and on Jan 20, 1898, a deputation from the Association waited upon the Secretary of State for War, Lord Lansdowne, and urged the desirability of forming a single Army Medical Corps It also expressed the hope "that Her Majesty might be graciously pleased to convert such a corps by Her authority into a Royal Corps, and to give it thereby a position and prestige to which it was fully entitled."[1]

University of London

The following degrees have been awarded

M.D—H B Hewitt.
M S—A J Davies

Mr A W Wilkinson, senior lecturer in surgery in the University of Aberdeen, has been appointed to the university chair of pædiatric surgery at the Institute of Child Health

Mr Wilkinson qualified M.B in the University of Edinburgh in 1937, and took the F R.C S E three years later In the 1939–45 war he served in the R.A M C in Europe and the Far East, gaining the rank of lieutenant-colonel as officer in charge of a surgical division Returning to Edinburgh, he held the Syme surgical fellowship from 1946 to 1949, when he was awarded the gold medal for his CH.M thesis He was appointed lecturer in surgery at Edinburgh in 1951 and senior lecturer at Aberdeen in 1953 He is at present an assistant surgeon to Aberdeen Royal Infirmary and to the Royal Aberdeen Hospital for Sick Children His published work includes a book, *Body Fluids in Surgery*, and articles and chapters in books on disturbances of electrolytes and of metabolism in surgical patients

Dr A G Spencer, first assistant at University College Hospital Medical School and consultant physician to University College Hospital, has been appointed to the university readership in medicine at St. Bartholomew's Hospital Medical College

University of Alberta

Dr T A S Boyd has been appointed associate professor of ophthalmology

Hunterian Society

The society's gold-medal essay competition for 1957 has been won by Dr C A H Watts (Leicester)

The subject for the 1958 essay is Impotence The competition is open to all general practitioners Details may be obtained from the hon secretary, Dr C W Kesson, 51, Harley Street, London, W 1

World Congress on Fertility and Sterility

This congress will be held in Amsterdam from June 7 to 13, 1959 Further particulars may be had from the secretary, Dr L I Swaab, Sint Agnietenstraat 4, Amsterdam-C

Mental After Care Association

The annual meeting of this association will be held on Wednesday, April 23, at 3 P M, at the Caxton Hall, London, S W 1, when General Wilfred Kitching, international leader of the Salvation Army, will give an address

Merseyside Medical Art Society

This society was inaugurated at a dinner on April 2, when Sir Philip Manson-Bahr, president of the London Medical Art Society, gave the opening address, to which Lord Cohen of Birkenhead and Prof Brian Maegraith, the president, replied. The first exhibition, held in the Bluecoat Chambers, included works by doctors in Liverpool, Manchester, Warrington, and Southport. The society's secretary is Dr D B Mossman.

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[1] *Brit med. J* Jan. 29, 1898, p 330

Memorial to Mr H R Segar

Mr H Roland Segar became medical superintendent of Barnet General Hospital in 1929 and medical director in 1949 He relinquished this post in 1952 but continued as consulting surgeon till his death A memorial to him is planned at the hospital, and subscriptions should be sent to Mr H D Cobbe, the treasurer, at 1, Wellhouse Lane, Barnet, Herts

Mental Health Research Fund

At the annual meeting on March 25, Lord Monckton, who is chairman of the joint national appeals organisation both of this fund and of the National Association for Mental Health, spoke of the need for the public to support research on mental disorder

"It would be easy", he said, "to criticise the Government for not devoting a larger proportion of what can be spent on research to medical research, but I have been too lately released from the Government stable to be ready to prefer this sort of criticism without going on to say what research now being undertaken ought to be abandoned to make way for this Then the criticism has been levelled that, when something between two and three million pounds is being spent by the Medical Research Council, it is wholly wrong to find them spending not more than £56,000 in the field of mental-health research in the year 1957–58, but here again I feel the difficulty (which has not deterred some critics) of pointing out what medical research funds are being spent for purposes that could be abandoned to make way for this" The real answer, he believed, lies in fostering and supporting a voluntary organisation "A marked and substantial *improvement in the response of individual members of the public* would be the most effective stimulus to further Government interest" The policy of the Fund had been to encourage more research-workers to enter this field by means of grants and fellowships, and up to last September in three years it had committed itself to spend no less than £50,000 But most of this money had come from generous contributions by the Ford Foundation, and other charitable bodies "It is, I think, a profoundly disturbing fact that, apart from such contributions, the donations and subscriptions from the British public, including broadcasts and flag-days, to the N A M H and the M H R F together, never reached £20,000 in any of the three years 1954–57"

Since last September a further £23,000 has been allocated by the fund to research projects, some being given for expenses and some *for fellowships The recipients are*

Dr Mildred Creak (psychosis in early childhood), Dr Ian Cameron (intellectual disintegration in senile dementia), Dr George Jacobides (puerperal psychoses), Dr G Ettlinger (establishment of a Primate Behaviour Research Laboratory), Dr Denis Parr (alcoholism), Mr Malcolm Piercy (cerebral localisation of intellectual function), Dr B W Richards (biochemical abnormalities in mental deficiency), Dr Michael Young (families of mental-hospital patients), Dr R T C Pratt (biochemical disturbance in endogenous depression), Dr J W B Douglas and Dr J Tizard (behaviour and social ratings of national 1946 sample of children), Dr T C N Gibbens (clients of prostitutes attending V D clinics), Dr B R Gomulicki (perception and learning in blind children), Prof E Stengel (suicide), Dr H H Wolff (psychotherapy in bronchial asthma), and Dr Steven Folkard (follow-up of patients discharged through review and rehabilitation unit)

Prof Georg Maurer, chief surgeon of the Munich hospital where members of the Manchester United football team were treated after the recent air crash, has been appointed an honorary C B E

Mr Arnold Walker has been re-elected chairman and Prof A A Moncrieff deputy chairman of the Central Midwives Board

Mr Derek Walker-Smith, the Minister of Health, has appointed Mr J T Woodlock to be his principal private secretary

A south-western branch of the Dental and Medical Society for the Study of Hypnosis is to be formed and a preliminary meeting for those interested is to be held at the Gloucester Royal Infirmary on Sunday, April 27, at 3 P M

A meeting of the Manchester Royal Infirmary Old Residents' Club will be held at the Midland Hotel, Manchester, on Saturday, Oct 4 All ex-residents will be sent particulars within the next few weeks

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CORRIGENDUM *Allergy to Cow's Milk*—In this annotation (Feb 8, p 304) we implied that observations reported by C Collins-Williams were made in the U S A, whereas in fact they were made in Canada

Royal Commission on Remuneration

The Royal Commission on Doctors' and Dentists' Remuneration will hold public hearings at 11 15 A M on April 24 and 25, at 10, Carlton House Terrace, London, S W 1 Representatives of the Royal College of Surgeons of England have been invited to attend on Thursday and representatives of the Royal College of Obstetricians and Gynæcologists on Friday

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Diary of the Week

APRIL 20 TO 26

Monday, 21st

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W C 2
5 15 P M Mr C P Wilson Malignant Disease of the Superior Maxilla
6 30 P M Sir Clement Price Thomas Carcinoma of the Bronchus.
UNIVERSITY OF LONDON
5 30 P M (National Hospital for Nervous Diseases, Queen Square, W C 1) Prof B D Burns (McGill) The Problem of Memory

Tuesday, 22nd

ROYAL COLLEGE OF SURGEONS
5 P M Mr I P Todd Physiology of Rectal Sensation and its Relationship to Disease (Arris and Gale lecture)
6 15 P M Mr Rodney Maingot Postoperative Strictures of the Bile Ducts
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
8 P M *Medicine* Dr E R Cullinan, Dr Ffrangcon Roberts, Dr R R Bomford The Physician's Obligation to Society
INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Dr P J Hare Lymphomata and Reticuloses
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W 1
5 30 P M Mr L C Oliver Contributions of Surgery to the Treatment and Understanding of Parkinsonism

Wednesday, 23rd

ROYAL COLLEGE OF SURGEONS
5 15 P M Mr H J Seddon Surgery of Poliomyelitis
6 30 P M Mr S O Aylett Ulcerative Colitis
INSTITUTE OF DERMATOLOGY
5 30 P M Dr J O Oliver Blood Changes in Skin Diseases
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P M. Mr O S Tubbs Surgery of Diseases of the Pleural Cavity

Thursday, 24th

ROYAL COLLEGE OF SURGEONS
5 15 P M Mr Wylie McKissock Surgical Treatment of Intracranial Aneurysms
6.30 P M Prof C G Rob Arterial Occlusion
INSTITUTE OF DERMATOLOGY
5 30 P M Dr W N Goldsmith Metabolic Disorders
MANCHESTER MEDICAL SOCIETY
8 P M (Staff House, University of Manchester) *Anæsthetics* Dr M W Johnstone Control of Surgical Shock

Friday, 25th

ROYAL COLLEGE OF SURGEONS
5 15 P M Mr N R Barrett Tumours of the Chest Wall
6 30 P M Mr Victor Riddell Management of Thyrotoxicosis
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W C 1
3 30 P M Dr Imrich Friedmann Advances in Chemotherapy in Ear, Nose, and Throat Diseases
ST MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W 2
5 P M Mr John Peel Modern Cæsarean Section

Appointments

BAINBRIDGE, JEAN M, M B Durh, D OBST deputy M O H and deputy principal school M O, *Gateshead*
BROOKS, D M, M B Dubl, F R C S I part-time consultant orthopædic surgeon (with special responsibility for hand surgery), Royal National Orthopædic Hospital, London
BURNFORD, A M, M B E, M B Lond, D OBST, D C H assistant M O, Nottingham
COTTOM, D G, M C, B M Oxon, M R C P physician, pædiatric department, St Thomas' Hospital, London
HIRD, GORDON, M B Aberd, D P H district M O H and port M O, Boston
LINN, J C, M B Lond, D M R D part-time consultant radiologist, Rotherham group of hospitals
McCONNELL, R B, M D Lpool, M R C P part-time consultant physician, Broadgreen Hospital, Liverpool
MANNING, C W S F, F R C S part-time consultant orthopædic surgeon and assistant clinical director, Royal National Orthopædic Hospital, London
PIPER, G W, M B Lond, D P H deputy M O H, Westminster and Holborn, London
WHITE, JANET M M B Lond, D C H assistant M O, Finchley and Hendon.
ZAUSMER, D M M B, B.SC, Lond, D P M consultant in child psychiatry, Birkenhead, Wirral and Chester hospital areas

Leeds Regional Hospital Board

BIRD, J D, M B Sheff, F F A R C S, D A part time consultant in anæsthetics East Riding group of hospitals and Hull Royal Infirmary
SMITH A L G, M B Glasg, D P M consultant in psychiatry, Storthes Hall Hospital Kirkburton, nr Huddersfield
WILKINSON N V, M B Durh D P M assistant psychiatrist (S H M O), Clifton Hospital, York, and associated clinics

The Lancet · Saturday 26 April 1958

SOCIAL MEDICINE IN DEVELOPING COUNTRIES*

CICELY D WILLIAMS
B A, D M Oxon, F R C P, D T M & H
FORMERLY ADVISER IN MATERNITY AND CHILD HEALTH, SOUTH EAST ASIA REGION, WORLD HEALTH ORGANISATION

SOME of the many definitions of Social Medicine imply that it deals chiefly with social pathology, with human beings in aggregates, and with statistical results But social medicine has its clinical application as well as its pathology It deals with individuals as well as with communities (The hermit in the wilderness and Robinson Crusoe on his island have their social attributes and implications) And there is much in human needs and experiences which cannot be expressed statistically

The fact that too great a reliance on statistics may be misleading has been shown most plainly in the developing countries, where social medicine has a great deal to teach and to learn, though statistics are at present often unobtainable Another lesson which work in these countries teaches us is the necessity, for social medicine, of a good follow-up service It is the only means of ensuring that diagnosis is complete and accurate, that treatment is adequate, and that complications and sequelæ are prevented Without it, money spent on medical services and medical researches may be squandered

The Ivory Hospital

In Europe and North America hospitals are the core of the medical world They started many centuries ago with high standards of what Milroy called "philanthropic benevolence" and they have grown into sanctuaries of scientific medicine And yet there are complaints about them Some say that the patients are submitted to a large number of investigations rather than to the individual care and human kindness which they need No one person seems to be responsible for the patient as a whole Often the teaching of students is almost entirely divorced from the realities of the circumstances in which the patient became ill and to which he will return on leaving hospital[1] Medical students and nurses during their training see mainly the institutional side of medicine they are largely unaware of the public-health services and of the social sciences In some hospitals the duty of the medical team is felt to be the application of the natural sciences, and the almoner, as an exponent of the social sciences, is excluded from her place in it

In some parts of the world medical services as a whole are backward At first sight one may be struck by the good physique of the people, but it is usual to find that the expectation of life is short, and mortality among children high The sick or sorry are not the ones to be seen swinging along the roads or laughing together in the market-place In other countries the medical services are uneven Hospitals may be found with the most modern equipment, and the most expert methods of treatment and research, while in other parts of the same town people live in squalor and disease, getting no advantage whatever from scientific medicine

In most of these countries the indigenous forms of medicine are by no means scientific In some all forms of ill health are ascribed to the malevolence of witches or to the machinations of enemies Prevention of accidents and treatment of disease generally include some sort of magical ritual At the same time these systems of medicine may employ some extremely useful drugs, and some highly expert forms of massage and manipulation They nearly all include a close personal faith in the individual practitioner, and a sympathetic understanding of the troubles of the patient.

Pill and Injection

In many regions scientific, or Western, medicine was first introduced as medical care for the expatriate European population Attention was focused on the major epidemic diseases, such as plague, cholera, and smallpox, which involve risks to all, and whose control requires both treatment and preventive organisation In the emergency of an epidemic the population must be dragooned into compliance with regulations, and there is little opportunity to employ the arts of education, persuasion, and the finer points of social medicine.

As conditions improve and these major epidemics are forgotten, attention turns to endemic diseases, such as malaria, yaws, leprosy, and filariasis Of late there has been vast improvement in the techniques for dealing with these conditions and a great many mass campaigns have been launched The basis of these campaigns is usually to devise measures that demand from the population passive acceptance rather than active cooperation People have been urged

> "Let us spray your house, this will prevent malaria"
> "Let us give you an injection, this will cure your syphilis and your yaws"
> "Let us inoculate you, this will protect you from tuberculosis"

This type of campaign has had a great deal of success It is easy to get some statistical measure of the work accomplished, which pleases the administrators Not much effort is required from the recipients, which pleases them. And those who conduct the campaigns have a sense of achievement The techniques need not vary greatly from country to country, so that little local knowledge is needed The auxiliary staff are recruited locally, and when they have mastered a few simple techniques they become valuable assistants

Sometimes these campaigns stimulate not only the control of a particular disease, but also other functions of the medical service Within a short time they may show significant results by lowering mortality and morbidity and by increasing production The campaigns may then become a spearhead for further improvements But they have a negative side which should not be overlooked They may prove costly in money and in personnel, the improvement in health may be only temporary unless campaign to control the disease is followed by continued endeavour, and the lowering of mortality may lead to an embarrassing increase in population Thus health measures may be effective and yet not improve standards of living, education, or responsibility The greatest danger is that people may get the impression that good health may be achieved by a pill or an injection They do not associate improvements with their own responsibilities or with alterations in personal and community behaviour

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* Abridged from the Milroy lectures for 1958, delivered before the Royal College of Physicians of London on Feb 4 and 6

[1] Grundy, F, Mackintosh J M *Wld Hlth Monograph* no 34, 1957

Even though malaria has been controlled and yaws eliminated, there will still be a great deal of ill health and inefficiency The population continues to demand (and the medical department attempts to supply) antimalarial drugs for every fever, and penicillin for every other disorder The community which demands pills and injections for every discomfort, but has not been led to take an interest in improving living conditions or food habits, is sometimes more difficult to reform than one which ascribes all illness to spells and incantations

One of the results of this attitude of mind may be a pressing but irrational demand for more medical services, a demand for quantity without any respect to quality The people insist on new dispensaries at C and D, while the dispensaries at A and B are allowed to fall into disrepair, before there are enough trained staff for either A new hospital is deemed to give prestige though the staff is so inadequately trained and supervised that it can scarcely be medically beneficial Men, and to a lesser extent women, attend as outpatients for trivial complaints, invariably asking for a bottle of medicine or an injection In a country that still has a great deal of ill health, a multiplicity of second-rate or third-rate medical establishments is a serious hazard to a constructive health policy

Responsible administrators are apt to develop a cynical attitude towards the medical department "The demand for hospitals is so great that I feel we are teaching the Africans to become a nation of hypochondriacs" was a comment on one area where scarcely half the children survive to maturity Can anyone really believe that it is hypochondria that kills half the children? Or has medicine failed to justify itself? Is bad medicine driving out good?

Diseases and Patients

The Western type of medicine is by no means always acceptable Many people still prefer the indigenous or non-scientific medical practices, largely because they are more sympathetic and perhaps only a little less efficient They only turn to Western doctors when they are desperate, or as a method of appeasing another powerful *mana* Their attitude towards hospitals and medical advice may remain entirely different from that of people who have grown up in contact with the resources of scientific medicine

All over the developing countries new schools and colleges of medicine are being set up which are based on scientific or Western teaching Yet one of the weaknesses of medical training in Europe is its neglect of the social sciences and of the social factors that affect the life and health of patients These overseas schools and colleges are too often dependent on the doctors trained in this European pattern If they are out of touch with social factors in their own countries, how much more is this not true in the countries of their adoption?

Some European doctors who go overseas make the most of their opportunities to learn the local patterns of living and of ideas The missions, for instance, aim at a continuity of staff which provides time and opportunity to learn the languages and get to know the people and their problems But in many of the Government and university posts this sort of continuity is not regarded as essential or even desirable

In recent years there has been a great increase in international travel Doctors from Europe and North America have visited hospitals and universities overseas They often mention with satisfaction the operating-theatres, laboratories, libraries, and pathological museums They rarely refer to the record-keeping, the patients' food, the casualty department, or follow-up service Sometimes they do not mention paediatrics It is natural, therefore, that insufficient attention may have been paid to these matters

The result is that while European medicine has been focused on institutions, medicine in developing countries has been largely focused on diseases Once a condition is recognised as being prevalent, it is labelled as "a public health problem", and approached by mass methods But mass surveys, mass treatment, mass feeding programmes, mass health education, and environmental sanitation are expensive and not always appropriate They cannot take the place of individual care, and of consistent and careful observation The old narrow view that by using specific techniques and curing specific diseases we would all achieve health has proved wrong It is a mistake to look only for mechanical answers to what are mainly human problems

Dangers of Specialisation

It is increasingly realised that the human being must be treated as a whole, and the family as a unit To disregard man in his environment or to ignore the importance of his place in the community or within the family is to invite complications Yet, with the rapid development of the biophysical sciences, medicine is more and more divided into highly specialised techniques Some of the specialisations lead to rapid advances in research, but some are shortlived and have only a limited contribution to make

The more a subject becomes specialised, the more it tends to pursue its own aggrandisement and perpetuation—sometimes irrespective of the general needs of the community, and the general resources of medical care Each procedure demands from the patient fresh personal contacts which are in themselves exhausting . Records have to be multiplied—collaboration becomes time consuming But the real danger arises when the narrow specialties try to direct policy and exclude the consideration of other important philosophies

In medicine the multiplication of workers has tended to separate the scientific from the social disciplines and preventive from curative medicine In this country we have a large, expensive, and elaborate medical organisation which has been remarkably successful in dealing with disease, disability, and incompetence, but it is based on strong historical traditions, on a highly industrialised society, established law and order, and on an acceptance of social responsibility If they go overseas, doctors and nurses who have trained in this country, may find it hard to adapt themselves to new conditions where the pattern of medical care is simpler and where they must be prepared to deal with large numbers of very common diseases The true need of the developing countries is for medical services with a broad outlook that will have curative, preventive, and social functions Too much specialisation is expensive and inappropriate Experience has shown that specialisation in certain diseases often leads to the neglect of others

At the administrative level, too, there is still an inclination to call in a new specialist for every problem If health education is needed, then a "health educator" is employed If malnutrition is recognised, then a "nutrition worker" is thought to be necessary Yet these experts may have little or no clinical training, and are often not qualified to give health education or nutritional treatment to individual patients It is said that the doctors and nurses are not trained, or not interested in, or have no time for these things If so, it is preferable to employ more doctors and nurses and to give them better training The health educator and the nutrition worker may indeed be of service at the community level, but doctors and nurses should remain responsible for clinical diagnosis and management

In some places where the medical services are accepted only reluctantly a social anthropologist is called in to investigate and analyse popular resistance Many of the observations made by the social anthropologists could well have been reported by the doctors and health nurses working in the area, if ever they had been encouraged to do so Doctors and nurses have a great advantage over the research-worker, who is often only able to define the status of a population with respect to resources and conventions A medical staff, who have gained the confidence of the people among whom they work and live, can also observe the dynamics They can observe the response to improved health, the reaction to changing opportunities, and the variations with which individuals and families adapt their behaviour to new concepts

Many social workers from overseas come to train in Europe Commonly they go home with the idea that an expensive pattern of social security is of the highest priority They may feel that institutions should be provided for delinquent, neglected, and handicapped children But in the United Kingdom over 60% of the children who have to be taken under care are derelict because of some problem in health, and in countries where disease is far more prevalent than here a very much larger proportion of so-called social problems are in fact due to ill health or neglected health In most primitive societies there is a tradition of kinship and family responsibility, and it is more important to build on this than to provide institutions

The progress of medicine in the developing countries must in fact depend largely on its social content. Too much specialisation has led to the separation of clinical and social work, but expanded medical services would lead to the prevention of social complications and disasters

Custom and Nutrition

Nutrition is closely bound up not only with economics and geography but also with social *mores* Too often nutritional diseases are attributed to an absence of food, and the fact that the nutritional state is the end-product of dietetic, infective, parasitic, psychological, and even purely social factors is overlooked

Wherever malnutrition exists, it is always the children who suffer most Because medicine in the developing countries has given so little attention to the children the existence and the gravity of malnutrition has been overlooked for too long

A number of surveys have been made, but they are of limited value They often concentrate on schoolchildren, an age-group which is relatively healthy Though they record the stigmata of chronic or past malnutrition they rarely include the acute case Few data are given about the factors that have led to the condition

In some places true food shortage exists Sometimes this shortage is permanent, but in many places it is seasonal It may be due to poor storage facilities It is sometimes due to improvidence The people know how to make biltong and pemmican, but custom demands that when game is killed in hunting, or when cattle are killed for a celebration, these should be eaten in vast quantities They know how to store their grain, and how to preserve green food for the dry season, but it is not done It is social custom which demands enormous feasting on certain occasions, but which tolerates near-starvation between whiles This is a pattern of behaviour which adults appear to enjoy but which has a serious effect on young children

Sometimes irrational religious or traditional sanctions are associated with food Eggs, for instance, which are known to be nutritious and digestible, and very useful in feeding young children, are almost universally avoided Strict vegetarians, such as Hindus, will not use them The Malays say they produce worms, in some parts of Africa they are said to induce sterility, in others they are credited with causing baldness, and in others again they are said to make the child into a thief In some places they are simply regarded as tasteless and useless except for sale to Europeans

Not only is the choice of food at fault Sometimes it is the preparation, presentation, and timing Good cereals may be used, but they are insufficiently ground, pounded, winnowed and cooked, so that they are indigestible Enormous quantities may be given at one meal, and sheer distension may impede digestion and absorption

In some parts of the world children are given food that is so highly seasoned with pepper that its effect on the mucosa must be excoriating I am often told "But he is used to it", but nobody can say how many children have died in the process of "getting used to it"

In all the countries where malnutrition is common it will be found that there is much dyspepsia and gastro-enteritis among the children The dyspepsia often passes unnoticed, because the parents regard gross abdominal distension and pain as normal in children at weaning The same may be true of attacks of diarrhœa and enteritis It is often hard to get adequate laboratory diagnosis, but some of these cases of diarrhœa are due in fact to the physical properties of the food which cause irritation This may, of course, render the intestines more liable to invasion by pathogens

There is still much uncertainty about the effect of helminths Heavy infection with the ancylostome is known to produce anæmia Some claim that Negroes have a considerable racial resistance to hookworm [2] This is difficult to believe I wonder whether it will not prove on closer observation that many people have an acquired immunity towards helminths Those who have had mild infection in their early years may therefore show greater immunity in later life

Roundworms are sometimes said to be harmful only when they are present in large numbers I have myself seen serious complications due to roundworms But I believe that when one can observe children over long periods it will be found that the presence of one or two ascaris in the intestinal tract of a young child may interfere with digestion and absorption to a degree that may seriously affect the nutritional state

Sometimes the distribution of the food within the family is at fault Sometimes the nutritional state is poor because of other disorders, among which may be conditions as diverse as tuberculosis, scabies, and maternal deprivation

A great deal of trouble and money is now being spent on increasing food-supplies The distribution of supplementary foods is being organised But the provision of supplementary foods is symptomatic, not ætiological, treatment It does not in itself teach parents how to care for their children, or how to select or prepare their food, nor yet does it treat or prevent recurrent attacks of dyspepsia, diarrhœa, or helminthiasis It is personal advice and encouragement from someone who has won the confidence of the patient that is the most potent source of education

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[2] Keller, A E, Leathers W S, Ricks, H C *Amer J Hyg* 1934, 19, 629

The most serious aspect of malnutrition in many places is not the absence of food, but that the doctors and medical auxiliaries have not been sufficiently trained to diagnose nutritional diseases, more especially in the early stages when they are still eminently treatable

There is lack of hospital facilities for children with malnutrition Even where there are beds for children, diagnosis and treatment is sometimes inadequate and there is little attempt to educate the parents Not enough is done to discover the basic causes behind the malnutrition, and the follow-up and continued supervision is poorly organised

Protein deficiency is now looked on as a serious and widespread nutritional defect, and a great deal of international effort and money is being devoted to the supply of more proteins on a massive scale I do not agree with Waterlow [3] when he says

> " The prevention and control of protein deficiency in man is limited by the lack of scientific knowledge, not only in agriculture but also in medicine and physiology "

For years we have known how to diagnose and prevent protein malnutrition, and how to cure all but the moribund patients It is not scientific knowledge that is lacking it is the will to organise the necessary services, and give adequate training to the necessary medical personnel

Thousands of pounds are spent each year on high-level scientific conferences, on elaborate research, and on mass methods of feeding But we fail to find methods of application and we fail to give help where help is needed More attention to the social aspects of nutrition would ensure better diagnosis of the causes, better facilities for treatment, and better supervision to prevent recurrence

(To be concluded)

ON THE FAT-MOBILISING ACTIVITY OF HUMAN URINE

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FIRST ASSISTANT

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PREVIOUS studies on obese people (Kekwick and Pawan 1953, 1956, 1957) have shown that if the calorie content of the diet is kept constant, the rate of weight loss varies considerably with alterations in the composition of the diet (fig 1) Evidence was also put forward to suggest that the decrease in body-weight could be accounted for by loss of body fat and water It appeared that a mechanism existed for controlling the mobilisation of depot fat which must be sensitive to changes in the composition as well as the calorie content of the diet Such a mechanism should be operating at its maximum during fasting, and if any hormonal agent were involved it should be detectable in the urine Indeed Weil and Stetten (1947) had already shown the presence of a fat-mobilising substance in the urine of fasting rabbits

It was decided therefore to study the effect on fat metabolism of urine collected from healthy people during periods of fasting For comparison, urine was obtained from the same subjects when taking a normal mixed diet Batches of urine were collected and extracted in an identical manner The extracts were injected into mice, which were used as the experimental animals throughout

Method of Extraction

Subjects were fasted for 36 hours, urine being collected during the last 24 hours of this period

The urine was acidified to pH 5 3 with hydrochloric acid, 2 vols of ethanol was added, and precipitation was allowed to proceed for at least 16 hours The precipitate was filtered off, washed twice with ethanol-water mixture (2 1) at pH 5 3, dried at room temperature, and extracted with 0 5% aqueous sodium carbonate It was then centrifuged and the supernatant fluid obtained This alkaline extract was reprecipitated at pH 5 3 with ethanol and the precipitate extracted again with sodium carbonate The solution was neutralised just before injection The final volume of extract was made up to 10 ml for each 24-hour urine sample

Results

Experiment I Effect of Extracts on Liver Fat Content

Three separate groups of mice were used with each extract tested The first group received 0 5 ml of normal saline, the second 0 5 ml of urine extract from people taking a normal diet, and the third 0 5 ml of urine extract from the same people when they had been fasting All injections were given subcutaneously and the animals were killed after a 6-hour fast The liver fat was then estimated by the method of van de Kamer et al (1949)

It is clear from table I that, in every experiment, the urine extracts obtained during fasting produced a significant increase in liver fat Animals receiving the urine extracts from the same people when on a normal diet had liver fat values very similar to those found in the control animals The increase in liver fat was linearly related to the dose of urine extract over the range 0 025–2 5 ml per 100 g (table II, col 2, and fig 2)

Since many substances can produce fatty livers in animals through a toxic effect on the liver itself, further evidence was needed to support the view that the effect of the fasting urine extracts was due to increased mobilisation of fat from the fat depots Table II (cols 3, 4, 5) shows the effect of fasting extract on blood-lipids It can be seen that phospholipids, cholesterol, and " total lipids " all increased more or less progressively with increasing doses of extract Further confirmation of the presence of fat mobilising activity in the extracts was obtained from studies in which radioactive fat was used

Experiment II Fat Turnover Studies

Mice were given a diet containing glyceryl tripalmitate-1-^{14}C (2 μC daily) for 3 days On the 4th day the animals received injections of saline or urine extracts After a 6-hour period, during which food was removed, the animals were killed and the fat separately extracted from the liver, subcutaneous tissue, intestine with mesentery, and the rest of the body (residual carcass) The concentration of ^{14}C (specific activity) in the fat from each source was measured in a windowless gas-flow counter

It was found that the activity of the liver fat was always much higher than that of the subcutaneous and residual, carcass fat in control animals injected with saline (table III) There was a large variation, owing presumably to differences in the amount of labelled fat ingested and absorbed by each animal The effect of the urine extracts was nevertheless remarkably well defined (fig 3) In the case of the subcutaneous and liver fat the values obtained with the non-fasting extract did not differ significantly from the controls The fasting extract, on the other hand,

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3 Waterlow J W *Ind med J* September, 1956, p 167

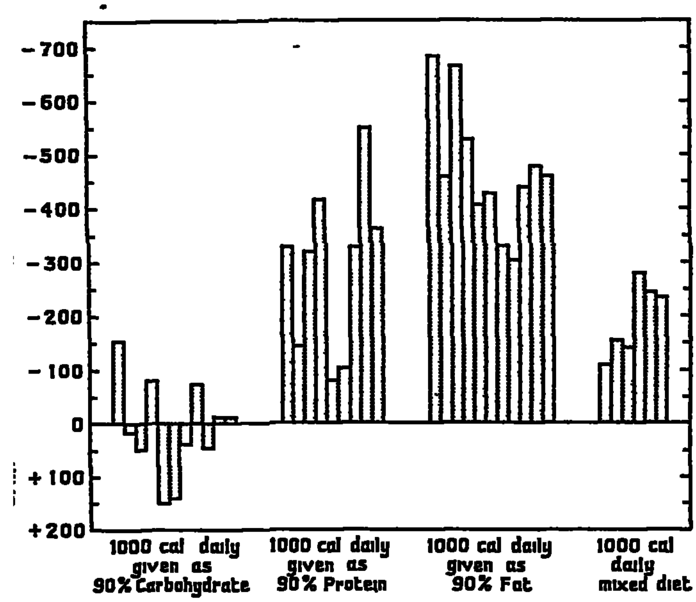

Fig 1—Effect of alteration in the composition of 1000-calorie diets on body-weight of obese people. Daily weight changes are the mean figures of 5-9 day periods on each diet.

produced a fall in the specific activity of the fat from both sources This extract also produced a fall in the activity of residual carcass fat as compared with saline The effect of non-fasting extract on residual carcass fat could not be determined clearly owing to the wide scatter in the results obtained

The total weight of subcutaneous and residual-carcass fat did not change appreciably Therefore the decrease in specific activity after the fasting urine extract seems to be due to an increased turnover of fat that is to say, both mobilisation and deposition of fat have been speeded up, the newly deposited fat being derived from unlabelled precursors An alternative interpretation must be mentioned that the recently administered fat, containing the radioactive label, had been more readily mobilised than the remainder of the depot fat This view could account for the fall in specific activity of the depot fat, and would be consistent with the failure to detect a fall in the total amount only if the actual quantity mobilised was too small to be measured

TABLE I—EFFECT OF INJECTIONS OF SALINE SOLUTION AND HUMAN URINE EXTRACTS ON MOUSE LIVER FAT

Source of urine	No of mice used	Liver fat %			% increase $\left(\frac{F-C}{C}\times 100\right)$
		Saline solution (C)	Non-fasting urine	Fasting urine (F)	
Individual collections					
1	15	3·6	3·8	4·6	22
2a	15	3·6	3·6	14·9	314
b	60	5·8	5·7	10·0	73
c	6	5·2	5·5	9·9	91
3	15	4·6	5·0	6·9	50
4	15	4·6	4·8	5·6	22
5	12	6·7	6·8	8·6	28
6	12	5·4	5·8	7·2	33
7	4	—	4·9	6·1	—
8	4	—	5·7	7·9	—
Pooled collections					
9–20	39	5·5	5·5	9·1	66
21–32	4	4·4	—	7·2	64
33–38	4	4·15	—	7·0	68

In the case of the liver, the increase in the total amount of fat after fasting extract must be taken into account. The fall in specific activity here must indicate dilution of the relatively strongly labelled liver fat by transfer of low-activity fat from the depots or increased hepatic synthesis of fat from unlabelled sources

Taken together, therefore, measurements of the concentration of ^{14}C in fat from different regions provide further evidence that the fasting extracts contain a fat-mobilising substance

Evidence was also obtained from this experiment that the effect of this material is not merely to transfer fat from the depots to the blood-stream and the liver but also to increase the rate of fat catabolism (Table II [col 6] shows that the blood ketones were increased following injections of the extract) When mice were fed radioactive fat for 3 days and on the 4th day killed 6 hours after an injection of saline, about 60% of the administered activity could be recovered in the body fat (table IV) After injection with urine extracts from people eating a normal diet, the percentage recovered was similar After injection with urine from the same subjects fasting, however, no more than 25–35% of the administered activity could be recovered as fat. Since the total amount of fat in these animals was not significantly less than in the controls, it appeared that the "fasting" urine extracts were capable of increasing the total metabolic turnover of fat in the animal as a whole

TABLE II—EFFECT OF GRADED DOSES OF "FASTING" URINE EXTRACT ON LIVER FAT, BLOOD LIPIDS, AND BLOOD KETONES 4 MICE WERE USED AT EACH DOSE LEVEL MEAN VALUES AND PERCENTAGE CHANGES COMPARED WITH THE SALINE CONTROLS

Dose of extract (ml.)	Liver fat g per 100 g	Blood lipids			Blood ketones (mg per 100 ml)
		Lipid phosphorus (mg per 100 ml.)	Total cholesterol (mg per 100 ml.)	"Total lipids" (mg per 100 ml.)	
Saline solution	3·9 (0)	5·4 (0)	57 (0)	430 (0)	0·9 (0)
0·01	4·1 (+5)	5·9 (+9)	53 (−7)	458 (+7)	1·5 (+66)
0·1	5·6 (+44)	6·1 (+13)	60 (+5)	500 (+16)	2·2 (+144)
1·0	7·1 (+82)	6·7 (+24)	63 (+10)	495 (+15)	2·6 (+189)
10·0	7·5 (+92)	7·1 (+31)	79 (+38)	580 (+35)	3·9 (+255)

Experiment III Effects of Repeated Injection on Body-weight and Carcass Composition

Three groups of mice were injected subcutaneously on alternate days for 17 days—the first group with saline solution,

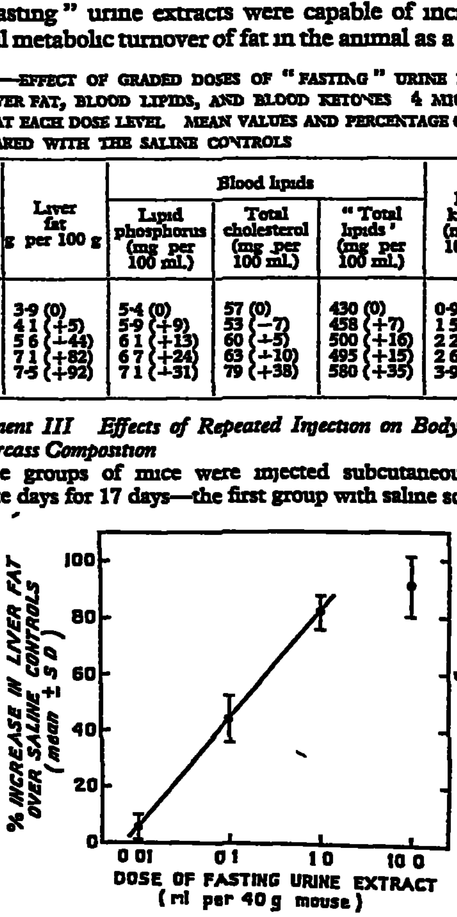

Fig 2—Dose-response curve (semi-logarithmic) showing effect of fasting urine extract on liver fat content (4 mice at each dose level)

TABLE III—SPECIFIC ACTIVITY OF FAT EXTRACTED FROM VARIOUS TISSUES AFTER FEEDING GLYCERYL-TRIPALMITATE-1-^{14}C 2 MICROCURIES GIVEN DAILY FOR 3 DAYS TO 20 MICE ANIMALS KILLED ON THE 4TH DAY 6 HR AFTER AN INJECTION OF SALINE SOLUTION

—	Counts per min per mg fat (mean ± 2 S E M)
Liver	997 ± 92
Intestine and mesentery	702 ± 164
Subcutaneous tissue	183 ± 16
Residual carcass	252 ± 28

the second with urine extract from people on normal food intake, and the third with extract from the same subjects when they had been fasting

Table v (col 4) shows that the group injected with saline solution lost a little weight, possibly because of the handling of the animals The group receiving the non-fasting urine extract also lost a little weight With the fasting urine extract there was a significantly greater mean loss of weight, amounting to over 6 g per mouse at the end of 17 days This finding again might signify no more than that the fasting urine extract contained a substance toxic to mice The animals, however, remained ostensibly in good condition, in particular, their appetite was unimpaired (Medical Research Council diet no 41 was fed ad libitum the difference between the weight of food offered and the weight remaining gave the amount consumed) This seems to be strong evidence against the presence of a toxic substance in the fasting urine extract Such a substance would be expected to impair appetite to a measurable degree

TABLE IV—EFFECT OF SINGLE INJECTIONS OF "FASTING" URINE EXTRACTS IN INCREASING TURNOVER OF WHOLE BODY FAT SERIES A (60 MICE) RECEIVED EXTRACTS 2B (TABLE I), SERIES B (49 MICE) POOLED EXTRACTS 9–20

Material injected 6 hr previously	Fat extracted from whole carcass, including liver			
	Total amount of fat as % of saline control (mean and S E D)		% of injected ^{14}C recovered (mean and S E M)	
	Series A	Series B	Series A	Series B
Saline solution	100	100	60 0 (±7 1)	52 6 (±8 9)
Non-fasting urine extract	98	94 (±11)	50 8 (±9·4)	59 5 (±14 8)
Fasting urine extract	111 (±11)	105 (±6)	37 2 (±4 1)	25 3 (±4 0)

The animals were killed at the end of the period and the carcasses analysed Table v, col 5, and fig 4 show that the weight-loss was entirely accounted for by loss of fat and water

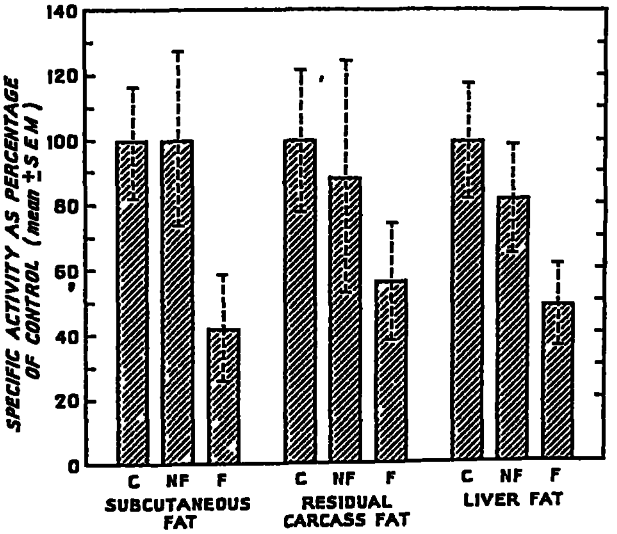

Fig 3—Effect of urine extracts on specific activity of subcutaneous, residual-carcass, and liver fat C, saline control, NF, urine extract (non-fasting) F, urine extract (fasting)

It is, we contend, reasonable to assume from this experiment that extracts from urine of people who have been fasting contain a substance capable of accelerating fat catabolism in mice, producing loss of weight without any significant reduction in the calorie intake of the animals and without any apparent impairment of their health or appetite

TABLE V—EFFECT OF REPEATED INJECTIONS OF SALINE OR URINE EXTRACT ON BODY WEIGHT AND CARCASS COMPOSITION EACH ANIMAL RECEIVED 0 5 ML ON ALTERNATE DAYS OVER A 17-DAY PERIOD

(1)	(2)	(3)	(4)	(5)		
Material injected (volume (0 5 ml)	No of animals	Mean food intake (% of control)	Body-weight change (g per mouse per day) (mean ± S E M)	Carcass analysis (% body weight)		
				Fat	Water	Protein
Saline solution	30	100	−0 109 (±0 055)	13 5	64 3	11·9
Non-fasting urine extract	10	101	−0 118 (±0 042)	13 4	63 7	11 8
Fasting urine extract	20	98	−0 360 (±0 049)	11 8	66 1	13 6

Experiment IV Examination of Urine Extracts by Paper Chromatography

Attempts were then made to identify the active substance The two extracts, one from people taking a normal diet and the other from the same people after fasting, were examined by paper chromatography When acetic-acid/water mixtures were used as the solvent, a substance was found in the fasting urine extract which was absent from the non-fasting extract This could be located with ninhydrin

Larger amounts of material were separated by chromatography and then eluted from the paper The eluate was dried and made up to the original volume as applied to the paper This material was injected into mice and again found to increase the liver fat (table VI) The remainder of the paper and, in particular, adjacent areas were separately eluted and these eluates injected into mice Table VI also shows that the active substance was absent from other parts of the paper

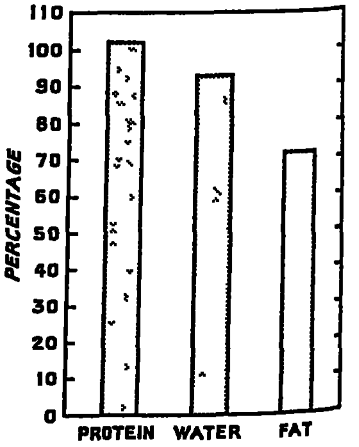

Fig 4—Total body protein, water, and fat of mice who had received fasting urine extract over a 17-day period, expressed as % of initial values (Initial composition of experimental group assumed to be the same as final composition of control groups)

It appeared possible, therefore, by means of paper chromatography to separate material from the urine extracts of healthy people who had been fasting which was absent from the urine of the same subjects taking food This partially purified material had the property of increasing the fat content of the livers of mice, under the same conditions as in experiment I

TABLE VI—EFFECT ON LIVER FAT OF ELUATES FROM VARIOUS PORTIONS OF THE FASTING URINE CHROMATOGRAM

—	Mean liver fat (g per 100 g liver)	% increase
Saline control	5 1	—
Urine extract F	8 7	71
After chromatography		
Saline control	5 1	—
Active ' spot	7 7	51
' Tail " of spot	5 5	8
" Inactive ' paper	5 3	4

Other Investigations

Preliminary investigations were also undertaken to determine whether this substance was present in human urine in other conditions associated with weight-loss, besides complete fasting

In three obese patients, who were kept throughout periods of 2 or 3 weeks on diets of equal calorie value (1000 calories), weight-loss was greatest when the calories were given mainly in the form of fat, losses were smaller with high-protein diets (table VII) When carbohydrate made up the major part of the calorie intake, little or no weight was lost (cf fig 1) When urine extracts were tested in mice, it was found that activity in the liver-fat test was again greatest during the high-fat periods and least during high-carbohydrate periods Moreover, material resembling that found in fasting urine could be demonstrated in the urine by paper chromatography during high-fat and high protein periods, but could not be detected when calories were supplied in the form of carbohydrate

Data on two patients with widespread malignant disease, one of whom was taking a fairly normal diet, are also included in table VII In both patients the urine was active in increasing mouse liver fat and the chromatogram was positive

Conclusions

It is conceded that any one of these experiments viewed in isolation is open to a different interpretation from that offered and indeed to possible objections Nonetheless, when the evidence is examined as a whole, it is difficult or impossible to escape the conclusion that a substance or substances exist in the urine of healthy people who have been fasting, and probably in other conditions, which has the properties of mobilising depot fat in mice, increasing the amount of fat in the liver, and increasing the rate of fat metabolism This substance, when given over a period of time, produces loss of body-weight in the animals without impairing their appetite

TABLE VII—EFFECT OF URINE EXTRACTS ON MOUSE LIVER FAT AND RESULTS OF CHROMATOGRAPHY IN 3 OBESE PEOPLE ON 1000-CALORIE DIETS AND IN 2 PATIENTS WITH MALIGNANT DISEASE

(1) Patients (all female)	(2) Diets	(3) Body-weight change (kg per week)	(4) % increase in mouse liver fat	(5) Chromato-graphic evidence
1 Obese	90% carbohydrate 90% fat	−0 8 −2 8	7 47	0 +
2. Obese	90% carbohydrate 90% fat 90% protein	−0 4 −2 5 −0 5	2 73 39	0 + +
3 Obese	90% fat 90% protein 90% carbohydrate	−2 3 −0 8 +0 1	65 50 13	+ + 0
4 Terminal malignant disease	Appetite very poor	−1·9	69	+
5 Carcinomatosis (breast)	Eating fairly normal diet	−0 4	43	+

Summary

A substance or complex is present in the urine of healthy people who have been fasting, which on injection into mice

1 Increases the total amount of fat in the liver

2 Mobilises fat from the fat depots

3 Appears to increase the total metabolic turnover of fat in the animals

4 Causes weight-loss without depressing appetite when given over a period of time, the loss being in the form of body-fat and water

The active material has been partially purified by paper chromatography

This substance or complex cannot be detected in identical extracts made from the urine of the same people when they are taking a normal diet

The substance, called here fat-mobilising substance, seems to be present in the urine in certain conditions, besides fasting, associated with weight-loss

We should like to acknowledge our indebtedness to the clinical research committee of the Middlesex Hospital for so generously placing facilities for keeping animals at our disposal, and to Mr A C Catchpole for his assistance in looking after them, to Sir Charles Dodds for his advice and criticism, and to Dr J F Tait for his advice on radioactive technique

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STAPHYLOCOCCAL PERITONITIS IN THE NEWBORN

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MINOR staphylococcal infections in the neonatal period have been increasingly reported in recent years Forfar et al (1953), commenting on this increase, drew attention to the potential dangers of such infections Reports by Sullivan (1956), Disney et al (1956), Beaven and Burry (1956), and Forbes and Emerson (1957) suggest an increasing incidence of staphylococcal pneumonia in young infants in Australia, Britain, New Zealand, and the United States respectively

Although in this age-group there is an increased incidence of all staphylococcal lesions, no report on staphylococcal peritonitis can be found in the English literature over the past ten years Nana and Mircioiu (1948) reported two cases of primary enterococcal peritonitis, and Ryan (1953) cited one case of primary staphylococcal peritonitis at the Edinburgh Royal Infirmary in 1929–53

Five cases of staphylococcal peritonitis in the neonatal period are now reported because the clinical picture was constant enough to make diagnosis possible in the three later cases These babies were all admitted to the Christchurch Hospital in the two years before July, 1957

Case-reports

Case 1—A boy, aged 14 days, born at full term, was admitted on April 29, 1956, with twenty-four hours' history of refusal to feed, pallor, and abdominal distension

On examination he was pale, listless, and acutely ill, with grunting respirations, peripheral cyanosis, and a uniformly distended tender abdomen. Bowel sounds were absent Scattered papules and two pustules on the legs suggested staphylococcal septicæmia The chest was clear on auscultation

Treatment was started with oxygen, penicillin, and intramuscular chloramphenicol, but the baby died in three hours

Necropsy revealed well-marked generalised peritonitis due to *Staphylococcus aureus* resistant to penicillin and the tetracyclines, but sensitive to other antibiotics

Case 2—A girl, aged 20 days and weighing 5¹/₂ lb, who was born three weeks prematurely, was admitted on Aug 20, 1956, with thirty-six hours' history of listlessness and twelve hours' history of vomiting Severe abdominal distension had been noticed during the twelve hours before admission, but only one offensive motion had been passed Greatly reduced bowel sounds were heard over this distended tympanitic abdomen

Treatment—A provisional diagnosis of meconium ileus led to treatment with subcutaneous fluids and laparotomy Operation by Mr J Ardagh revealed purulent peritonitis Despite a diligent search no local cause for this was found Peritoneal swabs grew *Staph aureus* resistant to penicillin and the tetracyclines but sensitive to chloramphenicol and erythromycin Treatment with intramuscular erythromycin 100 mg six-hourly was started After a stormy postoperative course, with an infected wound and severe anæmia requiring infusion with packed red cells, the baby was discharged on Oct 9, 1956 There was no history or evidence of antecedent skin infection

Case 3—A girl, aged 13 days, was admitted on Dec 6, 1956, with twenty-four hours' history of refusal to feed and vomiting For two days she had had no bowel motion, and increasing abdominal distension had been noticed

On examination her abdomen was tender and distended, and bowel sounds were absent No skin lesions were detected after careful search

Treatment—Primary staphylococcal peritonitis was diagnosed, and laparotomy and drainage of the abdomen were done Peritoneal swabs grew *Staph aureus* resistant to penicillin and streptomycin but sensitive to all other antibiotics tested Intravenous aureomycin 250 mg b i d was first used, and then erythromycin 100 mg six-hourly, both orally and by intramuscular injection

Progress—Recovery was slow and complicated by staphylococcal subcutaneous abscesses, hence the baby was not discharged from hospital until Jan 23, 1957

Case 4—A girl, aged 21 days, had developed in the first week of life a small pustular lesion on her left hand This lesion had been incised and painted with 1% gentian-violet solution She was admitted to hospital on Jan 26, 1957, with a week's history of apathy and forty-eight hours' history of increasing abdominal distension and vomiting

On examination she was pale and breathless, with distended tympanitic abdomen in which no bowel sounds were heard

Treatment—Staphylococcal peritonitis was provisionally diagnosed and treatment with intravenous erythromycin and fluids started, but the baby died within three hours of admission

Necropsy confirmed the staphylococcal peritonitis and revealed also a liver abscess The *Staph aureus* was resistant to penicillin, streptomycin, and the tetracyclines but insensitive to chloramphenicol and erythromycin The necropsy findings showed that umbilical infection had spread to the liver and peritoneum, despite the absence of any clinical evidence or history of umbilical sepsis

Case 5—A boy, aged 7 weeks, was admitted on Nov 14, 1957, with three days' history of abdominal pain He had not had any skin lesions, but his mother had had mastitis severe enough to necessitate weaning a few days before the onset of the baby's illness

On examination the baby had a high swinging temperature, and distended abdomen, with reduced bowel sounds

Treatment—Laparotomy five days after admission revealed generalised peritonitis, which gave a heavy growth *Staph aureus* only partially sensitive to penicillin but sensitive to all other antibiotics tested Considerable improvement followed six days' treatment with chloramphenicol Convalescence was complicated by subcutaneous abscesses, suggesting spread of the infection via the blood-stream

Discussion

In the five years before 1955 there were few recorded deaths from staphylococcal pneumonia or septicæmia in infants admitted to the Christchurch Hospital Since Beaven and Burry (1956) reported an explosive outbreak of staphylococcal pneumonia in newborn babies in a Christchurch maternity hospital there has been an increased number of all staphylococcal infections in this age-group From that date (December, 1955) to July, 1957, thirty-five newborn babies were admitted to the Christchurch Hospital with staphylococcal infections Five of these had staphylococcal peritonitis and showed a remarkably constant clinical picture The following features enabled a strong provisional diagnosis of staphylococcal peritonitis to be made in the last three cases (1) a history of vomiting unassociated with diarrhœa, (2) a tender distended tympanitic abdomen with reduced or absent bowel sounds, (3) pre-existing staphylococcal skin lesions (present in case 4 and in case 5's mother)

In case 4 the infection was probably via the umbilical cord, because histological sections of the cord showed bacteria and a liver abscess was present, but there was no superficial evidence of umbilical sepsis on clinical examination

In the other cases it is reasonable to assume that the bacteria were blood-borne (no blood was cultured) A previous history of staphylococcal infection would suggest septicæmia

These cases of peritonitis did not develop before the 14th day of life Murray et al (1953) have shown that transmitted maternal antibodies appear to protect the baby in the first 2 weeks of life

Differential diagnosis—Rickham (1955) reported 17 cases of peritonitis in newborn babies in three and a half years and suggests that peritonitis is not rare in this age group The more common causes are perforated or gangrenous bowel and meconium ileus, but staphylococcal peritonitis is one cause of acute bacterial peritonitis and should be considered when there is a history of other staphylococcal lesions The tympanitic silent abdomen should prevent confusion with respiratory infections in these cyanosed and distressed babies, who often had rapid grunting respirations

Treatment—Adequate treatment with the correct antibiotic seems to influence the prognosis, and on present knowledge erythromycin 150–200 mg per kg of body weight daily, alone or in combination with novobiocin 100 mg per kg of body-weight daily, is preferred Laparotomy in cases 2, 3, and 5 allowed drainage of the pelvis and is necessary to exclude the commoner causes of peritonitis Dehydration and electrolyte imbalance from vomiting may need to be corrected before operation In severely shocked and collapsed babies there is a place for the use of intravenous hydrocortisone

Summary

Five cases of "primary" staphylococcal peritonitis in newborn babies are described

A silent or near silent abdomen which was tender, tympanitic, and distended was uniformly present

This uniform picture and the preceding history were helpful in diagnosis

I wish to thank Dr J F Landreth, senior pediatrician, Christchurch Hospital, under whose care these cases were admitted, for his interest and helpful criticism and for permission to publish, Mr J Ardagh, who operated on cases 2 and 3 and has also offered

helpful criticism, and Dr D T Stewart, director of the department of pathology, for the necropsy reports

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"ENCEPHALITIS TREMENS"

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Two outbreaks of encephalitis with widely differing features and natural history have lately been described, one from Sierra Leone (Rose 1957) and the other from a London hospital (Medical Staff of the Royal Free Hospital 1957) We here record 25 cases of encephalitis seen at the Methodist Mission Hospital, Ilesha, Western Nigeria, which presented with characteristics different again, but in which the clinical picture was so distinct as to suggest a pathological unity Neither of us had seen such a condition before and in spite of the interest, advice, and generous help of many colleagues we have been unable to come to any proven conclusions about its ætiology

Incidence

The hospital serves a rural town of about 75,000 population, and a district of about the same population again During the last two weeks of September, 1956, 14 patients were admitted with a syndrome whose chief feature was tremor, and during the latter half of October, a further 11 patients were admitted with the same condition That all 25 cases formed a clinical unity, one could not doubt, for they were strikingly similar in many respects Since we became aware of the condition, we have been able to trace the records of sporadic cases in the same months of previous years, and last year (1957) more cases were seen

All the patients recovered, and we have therefore no necropsy findings, and though the epidemiology of the condition has been studied in some detail we have not been able to form any definite opinions about it

Clinical Features

These are best illustrated by the history of one of the earlier patients

A Yoruba woman (case 3), aged 24, was admitted to the hospital at 9 A M, Sept 17, 1956 She had, it seemed, been perfectly well until 8 A M the previous day, when she suddenly complained of headache and dizziness A little later she vomited, and there was also some colicky abdominal pain, but no diarrhœa After this she could not remember what happened, but relatives said that she started to " shake all over ", and that though she appeared able to hear questions and commands, she was unable to reply to them

She had a gross, coarse, rhythmical tremor of the entire body, exaggerated by sitting up and especially by standing She was conscious but unable to speak Her temperature was 99·2°F She was treated with mephenesin and magnesium sulphate by mouth, and bed rest Lumbar puncture yielded an entirely normal fluid

Next day she recovered her speech, and on the fourth day the tremors finally disappeared

The detailed histories in the other cases are given in the table, in sum, they were all characterised by

(1) Sudden onset of giddiness, followed by
(2) Vomiting, with or without abdominal pain, followed by
(3) Generalised tremors, which might or might not be followed by
(4) Aphasia, or unconsciousness (semicoma), or both

Onset of giddiness—The onset was always sudden, and no patient complained of antecedent illness Usually within an hour of the giddiness came vomiting, though in no case was this protracted and, in practically all, it had ceased on arrival at hospital Soon after the vomiting, tremor began

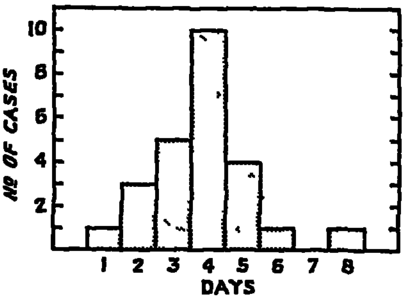
Tremor was the most dramatic feature of the syndrome It varied widely in severity, but had common features in all the patients Thus, it was generalised (affecting the head as well as the limbs and the trunk), rhythmical, and coarse It was exaggerated by sitting up, or by any attempt at movement and might become violent if the patient attempted to stand up The tongue often showed a similar tremor and in several cases the eyes showed conjugate and horizontal spontaneous

CLINICAL SUMMARY OF 25 PATIENTS

Case no	Age and sex	Onset	Presentation	Duration (days)	Vomiting at onset	Aphasia	Semicoma	Neck rigidity	Maximum temp (°F, axillary)	Maximum blood-pressure (mm Hg)	Retention of urine
1	8 M	5 A.M, sudden	Giddiness	4	N R	Nil	Nil	N.R.	100·0	N.R.	
2	25 F	Noon ,	,,	4	Present	Present	,,	Slight	99·6	90/60	
3	24 F	8 P M. ,	,,	3	,,	,,	,,	N R	99·4	N.R	
4	36 F	8 P M. ,,	,,	6	,,	,,	Present	,,	99·2	,,	
5	37 F	11 P M. ,,	,,	2	Twice only	,	8 days	Mild	100·4	90/60	
6	8 F	A.M. ,,	Tremor	8	Present	1 day	Nil	N R.	100·4	N.R.	
7	50 F	1 P M ,	,,	5		Present	12 hours	Mild	100·0	126/80	
8	40 F	2 A.M. , (woken up)	,,	5		Nil	Nil	,,	99·4	120/60	
9	28 F	4 P.M ,,	Giddiness	3	,	,,	,	Nil	100·4	108/76	
10	3 F	11 P M , (woken up)	Tremor	4	,,	Present	3 days	,,	100·0	N R	At onset
11	2½ M	11 15 P M (woken up)	,,	2	N R	Nil	2 days	,	N A	,,	
12	36 F	2 P M sudden	,	1	Nil	,	Nil	Mild	99·6	100/50	
13	18 F	5 A.M ,,	Giddiness	3	Present	,,	,,	Nil	99·0	96/68	
14	12 M	Midnight ,	Vomiting	3		,	,	,,	99·0	N.R.	
15	30 F	2 P M ,,	,,	4		,	,,	,	99·4	116/?	
16	45 M	N R	N R.	5	N.R.	,	,	,,	99·0	134/90	
17	35 M	2 A.M., sudden	Giddiness	4	Repeated	,,	,,	,,	99·6	N R.	Transient For 2 days
18	26 F	4 A M ,,	,	3	Present	,	,	N R.	101·6	,,	
19	13 M	P M. ,	Vomiting	2	,	,,	,,	,	99·6	,,	
20	39 M	11 P.M ,, (woken up)	Tremor	4	7 hr later	,,	,	Nil	99·0	140/98	
21	32 F	P M ,	,	5	Nil	,	,,	N R	99·6	130/80	
22	30 F	Midnight ,,	Giddiness	4	Present	Speaks with difficulty	Dazed	,,	99·0	N R.	
23	42 M	3 A.M ,,	,	4	,,	Nil	Nil	,	98·8	,,	
24	24 M	8 P.M ,,	,,	4	12 hr later	,,	,	Nil	98·4	124/64	
25	54 M	7 P.M. ,,	Tremor	4	Retching only	Present	,,	,,	103·0 (Transient —3rd day)	112/70	

N.R =not recorded. N A =results not available oscillations All the movements abated on lying down, and disappeared during sleep Left to pursue their own course (as in many of the later cases) the tremors abated in four or five days (see figure), their duration had no relation to their initial severity Though often complaining of some residual headache, the patients thereafter appeared perfectly well, and in no case was any personality change noticed by the relatives

Consciousness —Throughout the period of tremor, many patients were mentally alert and able to speak normally, though the tremor rendered them extremely ataxic and unable to walk without support *In 8 cases, however, there was an aphasia of motor type, the patients apparently being able to hear and* understand questions and commands but unable to reply In 5 cases there was unconsciousness (semicoma), only painful stimuli drew a response, with an exaggeration of the tremor Although this semicoma lasted alarmingly in one child for eight days, its duration was usually short, and the patients returned rapidly to normal consciousness once recovery started, with no intervening period of confusion and no retrograde amnesia



Duration of tremor from onset

Speech defect —When it occurred, the defect appeared to be a true aphasia of motor type for these patients could plainly *understand commands, and their sensory perception appeared* to be normal Furthermore, physical examination showed no other abnormality of motor power in the distribution of the cranial nerves, and lip movements were normal

Fever —Many patients had a low fever in only 5 did this exceed 100°F (and then transiently), and in the majority, the temperature did not exceed 99 4°F (axillary)

Muscle tone was usually normal, or somewhat reduced, though a mild neck rigidity was noted in some at the onset

Of the *reflexes*, the abdominals could not be elicited in many patients, nor in some the knee and ankle jerks, but, in general, tendon reflexes were present and symmetrical 3 patients had transient *incontinence of urine*, and 1 needed catheterisation for two days No true nystagmus was seen in any, but conjugate oscillatory movements of the eye (of the type described above) were seen in several patients

Loss of consciousness necessitated, of course, careful adjustment of water and salt balance, but otherwise did not appear to affect the prognosis

Investigations

Lumbar puncture was performed in 12 cases, but in all a clear fluid of normal cell count and pressure was withdrawn and we gradually came to feel that it taught us little about the patients and was therefore better avoided

In 2 cases the *urine* was searched for alkaloid constituents which might point to a toxic origin, but in no case was any abnormality found

Serological examinations in 7 of the patients, by Dr James Portafield, of the virus research unit of the West African Medical Research Council, disclosed no abnormality to suggest that a virus was responsible

In fact, the condition has so far yielded little to clinical and pathological examination

Natural History

The syndrome, though *alarming*, was never fatal Both dizziness and vomiting were transient prodromal symptoms, and the vomiting was never sufficiently severe to lead to difficulties with water and salt balance The tremors were the most persistent as well as the most dramatic symptom, but they too, after a maximal onset, gradually abated and disappeared in the periods shown above Both the aphasia and the unconsciousness, where present, usually abated within three days, though in one child semicoma alarmingly persisted for eight days

Ætiology

Age and sex —All ages from childhood to adult life were represented (see table) (In this setting, any age over 20 tends to be inaccurately reported) The first part of the outbreak (14 cases, September, 1956) affected only children and women and we spent some time considering the possible significance of this The second group, however (11 cases, October, 1956) included 7 men

Timing and incidence —The outbreak was spread over a period of six weeks, and then abated, arising in two distinct "waves", which suggested an infection Conversely, however, when the times of onset were plotted (and the onset was always so sudden that this could be done), the vast *majority* were seen to lie between 7 P M and 5 A M Considering the fact that in this rural society the main meal of the day is from 5 P M onwards, these figures might suggest (if they have any significance at all) that the condition was of toxic origin An extraordinary coincidence of onset within half an hour of each other in cases 10 and 11 (who were cousins living in the same household and sharing the same food) may also suggest the same conclusion

Geographical distribution —It is of interest that all 25 patients came from Ilesha, and none from the surrounding district Ilesha is a typical densely populated Yoruba town The average number of occupants per house is of the order of 20, and in some houses *many* more Yet apart from cases 10 and *11 already mentioned, and cases 1 and 2 (mother and child)*, no 2 patients came from the same household, and the geographical distribution of patients did not point to an infection

Diet —No common factor in the patients' diets was discovered which might account for the condition There was some difficulty in recovering relevant specimens owing to the prevalent habit of finishing the food at any one mealtime But several specimens were nevertheless obtained, and analysis was kindly undertaken by Dr John Broadbent In no case was any abnormal alkaloid discovered and similar analysis of the urine of 2 of the patients failed to show any such substances being excreted

Serology —The investigations proved completely negative

The two obvious possibilities were an intoxication due to foodstuffs or other sources, and a virus encephalitis The scales seemed weighted in favour of encephalitis, but we cannot prove it The similar cases in the same months of other years—at a season when food habits are not subject to change—is another argument for the "infective" view

Discussion

Tremor was the most dramatic and characteristic feature The associated loss of consciousness and the aphasia, indicate that the lesion affects the cerebrum but the *rhythmical coarse tremors of the limbs*, and the oscillatory movements of the eyes suggest also an affection of the basal ganglia and the mid-brain This in turn suggests that, whatever the lesions may be, it is widespread and yet it is so constant on distribution that the clinical picture is remarkably uniform—a picture, moreover, which is associated with little or no change in the cerebrospinal fluid

The Lancet (1956) discussed a series of outbreaks of encephalitis, and suggested that several of these outbreaks might be grouped under the provisional title "benign myalgic encephalomyelitis" Although the term has been disputed, the classification seems at least to be temporarily valuable, in that it does cover a group of outbreaks with many common features

The Ilesha patients share three important features with that group

(1) In spite of a profound neurological disturbance, the cerebrospinal fluid remained normal in all

(2) No evidence of the causative virus (if such there be) could be found

(3) The outcome was uniformly benign

In clinical features and natural history, however, these patients present a completely different picture to that of "benign myalgic encephalomyelitis" About the only point of resemblance is "the curious jerky response of the affected muscles to volition" which, Acheson (1957) remarks, "may yet prove to be a further clinical manifestation of benign myalgic encephalomyelitis"

Summary

An outbreak of encephalitis in the Western Region of Nigeria in 1956 involved 25 patients over a period of six weeks The onset was abrupt, giddiness, followed rapidly by vomiting and characteristic tremors, were the main features of a remarkably constant clinical picture. Semicoma, aphasia, or both supervened in some patients Abnormal physical signs were few, and lumbar puncture was always negative, as were also the results of serological investigation The condition proved benign, with no permanent sequelæ Similar cases were found in the hospital records for the same season of previous years, and again in 1957

No definite conclusions could be drawn about the cause of the epidemic This syndrome was unlike anything that we—or the many colleagues we discussed it with—had seen before

Our thanks are due to our colleagues, Dr C A. Pearson and Dr David Cannon, of the Methodist Mission Hospital, Ilesha, who also saw these patients to Prof Alexander Brown, Dr M MacGregor, and Dr R Hendrickse of the department of medicine, University College, Ibadan, and to Colonel John Walters of the West African Medical Research Council, with whom the cases were discussed, to Dr John Broadbent, department of pharmacology, University College, Ibadan, who undertook the analysis of various foodstuffs, and to Dr James Portafield, virus research department, West African Medical Research Council, who undertook the serological investigations

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HEPATOJUGULAR REFLUX

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FILLING of the external jugular veins when pressure is applied to the abdomen of patients with heart-failure was first described by a medical registrar at the Middlesex Hospital (Pasteur 1885) Rondot (1898), who used bimanual compression of the liver, realised that Pasteur was wrong in believing the test to be pathognomonic of tricuspid disease, because he observed the reflux in patients who later were found at necropsy to have healthy tricuspid valves The test became known as the Pasteur-Rondot test or, more generally, hepatojugular reflux However, pressure anywhere on the abdomen, not only over the liver, will fill the jugular veins (Lian and Blondel 1925)

In estimating venous pressure by the clinical method (Lewis 1930) pressure on the abdomen is often used to determine whether a pulsation in the neck is venous or arterial in origin A venous pulsation is almost invariably altered by this manœuvre, an arterial pulsation is unchanged

For a long time hepatojugular reflux has been regarded as a sign of cardiac failure, it has been described as probably the earliest sign in chronic cor pulmonale (Gillanders 1949, Oram 1956) If a positive hepatojugular reflux can be taken to show cardiac failure when there is no other evidence, it is important to understand the mechanisms involved and the possible sources of error For this reason we investigated the hepatojugular reflux, measuring changes in the central venous pressure in the superior vena cava with an electromanometer

In routine practice the internal jugular vein serves as a reliable manometer (Lewis 1930), and is more reliable than the external jugular vein, which may give false readings (J McMichael, personal communication) Wiggers (1914), however, emphasised that the effective filling pressure of the heart cannot be determined simply by manometers equilibrated with atmospheric pressure, but that it must be calculated on the difference between pressures inside and outside the right atrium For this reason a differential manometer which provided the algebraic sum of venous and intrathoracic pressures was used

Material and Methods

(1) 6 healthy people and 2 patients with severe emphysema were studied lying flat A 24 lb lead weight with a surface area similar to that of the hand was placed on the abdomen, and the intrathoracic and intra-abdominal pressures were measured simultaneously

These measurements were obtained from water-filled open-ended plastic tubes in the œsophagus and stomach (Dornhorst and Leathart 1952) and recorded with capacitance manometers ('Minirack,' Southern Instruments Co) The reference point was 10 cm above the table Changes in chest circumference were recorded from a mercury-filled rubber-tube stethograph of the type described by Wade (1954) A simultaneous spirometric record was obtained by incorporating a potentiometer in a Benedict-Roth spirometer These four parameters were recorded simultaneously on a four-channel photographic recorder (Elmquist)

(2) 7 healthy people, 2 asthmatics with a normal circulation, and 14 patients with heart-disease (7 of whom had venous hypertension) were studied lying flat.

Intrathoracic pressure was measured through a water-filled polyethylene tube, about 100 cm long and 1 mm in internal diameter, passed through the nose into the œsophagus (Dornhorst and Leathart 1952) An identical tube was used to measure venous pressure so as to reduce differences in damping to a minimum This was introduced into the basilic vein of the left arm either through a needle or, under direct vision, through a small incision The tube was advanced to a distance previously determined by a surface measurement until the pressure record on the oscilloscope showed a response to coughing similar to a simultaneous œsophageal pressure record Then it was assumed to be in the superior vena cava

Pressures were recorded with capacitance manometers One of two reference points was used—either the sternoclavicular joint or the "phlebostatic axis"[*] (Winsor and Burch 1946)

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[*] The 'phlebostatic axis' is the line of intersection between a plane drawn through the mid axillary line and a plane passing at right angles to this at the level of the fourth intercostal space at the sternal edge

The reference point and the anteroposterior diameter of the chest are recorded with each figure A single 25 cm column of saline solution was used as standard for both manometers

The manometers recording central venous and intrathoracic pressure were used in conjunction as a differential manometer, the electrical output from one manometer being opposed to *that of the other (Lee et al 1954) Thus was arranged so that* the differential record—the "filling pressure"—was positive when the venous pressure was higher than the œsophageal pressure The two direct pressures were monitored on a cathode-ray oscilloscope and recorded together with the differential pressure and an electrocardiogram by a four-channel photographic recorder

Because it is difficult to maintain a constant pressure with the hand, the lead weight already described was placed centrally on the abdomen This particular weight was chosen because the subjective sensation was similar to that produced by compression with the hand of the physician attempting to demonstrate reflux Hultgren (1950), however, considered that a 15 lb weight approximated to the pressure with the hand

Results

Effect of Application of Weight on Breathing

When a weight was applied to the abdomen, the intra-abdominal pressure always rose The effect on intrathoracic pressure was variable not only from one person to another but also with repetition in the same person If the subject "accepted" the weight, without abdominal resistance, the chest had to take over some of the diaphragmatic share of ventilation Fig 1A shows that this new type of breathing, shown by the spirometer, was achieved by increasing the chest circumference The unchanged intrathoracic pressure indicated that the increase in chest circumference had compensated for the reduction in chest volume which resulted from the ascent of the diaphragm (shown radiographically by Lian and Blondel 1925) If the subject resisted, the weight was supported partly by descent of the diaphragm (fig 1B) The chest circumference was unchanged, the intra-abdominal pressure rose higher than in fig 1A, the intrathoracic pressure fell, and the spirometer showed that the intrathoracic volume had increased considerably

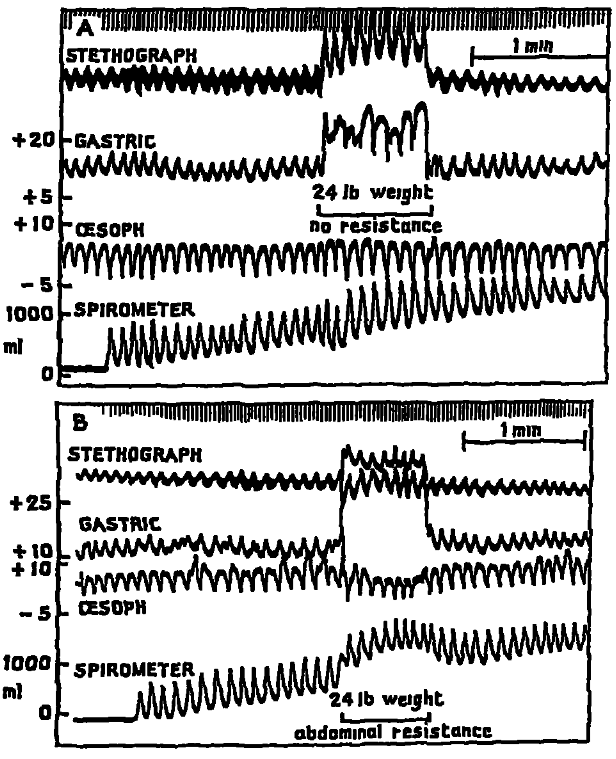

Fig 1—Simultaneous records obtained in healthy person during application of weight to abdomen A, without abdominal resistance; B, with resistance Note that in B gastric-pressure tracing crosses stethographic tracing during application of weight Reference point 10 cm anterior to back; anteroposterior diameter of chest 24 cm *Standards in cm saline Time marker lines, 2 sec*

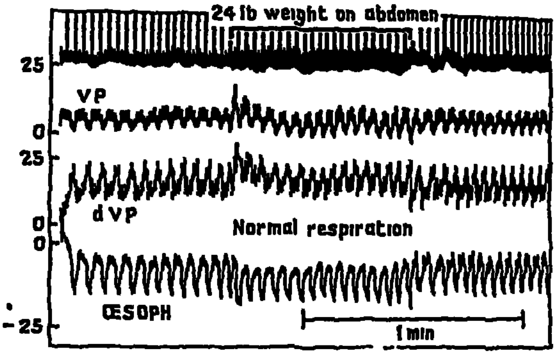

Fig 2—Healthy person: (from above downward) time marker (2 sec), electrocardiograph, V P, central venous pressure, dVP, differential or filling pressure; Œsoph, œsophageal pressure, as intrathoracic pressure *Reference point sternoclavicular joint; anteroposterior diameter of chest 20 cm*

It was impossible to predict the subject's response when no instructions were given about what he should do If the weight caused discomfort, he would resist If it did not, he tended to resist less with repetition as he found that breathing was easier if it did not involve moving the weight—i e, if it was more "thoracic" than "diaphragmatic" If instructions were given that he should not resist the weight, better repeatability was found, but even then there were significant variations in the results The chief relevant effect of resisting the weight is that it increases the pressure gradient across the diaphragm, which encourages the transfer of blood from abdomen to chest

In the 2 patients with emphysema the results were different Whether the patient resisted the weight or not, the effect of its application was to raise intrathoracic pressure In a further study of 7 patients with emphysema the intrathoracic pressure alone was recorded during the application of the weight to the abdomen The intrathoracic pressure rose considerably in 3, slightly in 2, and not at all in the remaining 2 In severe emphysema the chest is nearer the position of full inspiration throughout the respiratory cycle than it is in a healthy person The patient is therefore deprived of a mechanism for keeping the intrathoracic pressure at its resting level by further expansion of the chest In the 2 patients in whom the intrathoracic pressure remained unchanged the chest was probably capable of further expansion to compensate for the ascent of the diaphragm

Effect of Application of Weight on Central Venous and Filling Pressures

Normal—When the weight was applied to the abdomen in the 5 healthy people, there was a transient rise in venous pressure This rise was usually of short duration—e g, through three respiratory cycles (fig 2) *However,* there were minor variations which were due mainly to variations in the type of breathing response The venous pressure may even fall during the application of the weight if the subject breathes purposefully nearer his inspiratory maximum than normally There was then a greater than normal rise in filling pressure, reflecting the greater increase in venous return that results from the greater pressure gradient across the diaphragm The central venous pressure, however, fell after an initial small rise During the same type of breathing but without the application of the weight, the filling pressure still rose and the central venous pressure fell The initial peaks in both the central venous and filling pressures were lacking, indicating that application of the weight produces reflux of blood from the abdomen to the chest As already stated, the response altered with repetition However, to assess the situation accurately in any one person it would be necessary to have a simultaneous record of spirometer, stethograph, intra-abdominal pressure, intrathoracic pressure, and central venous and filling pressures Technically this was beyond our means

A fall in central venous pressure during the test was only seen in healthy people deliberately breathing near their inspiratory maximum The fall was then attributable to the fall in intrathoracic pressure The filling pressure always rose, usually for a short time

Cardiac failure—With heart-failure the extent and duration of the rise in venous pressure was greater than in healthy people An extreme example is shown in fig 3 In those people whose venous pressure was high at rest the response was similar In a "false negative" result the rise in filling pressure was not reflected in a rise in venous pressure, because the intrathoracic pressure fell There was, however, a gradation from the extreme example shown in fig 3 to the normal response In one patient, who had been orthopnœic and œdematous ten days previously, a normal filling pressure response followed treatment In a patient with mitral and aortic stenosis and a normal venous pressure the abnormal hepatojugular reflux was almost entirely attributable to an accompanying rise in intrathoracic pressure and was therefore a "false positive" Curiously and inexplicably, the only occasion on which we recorded an abnormal rise in filling pressure with a normal resting venous pressure was in an athletic medical student.

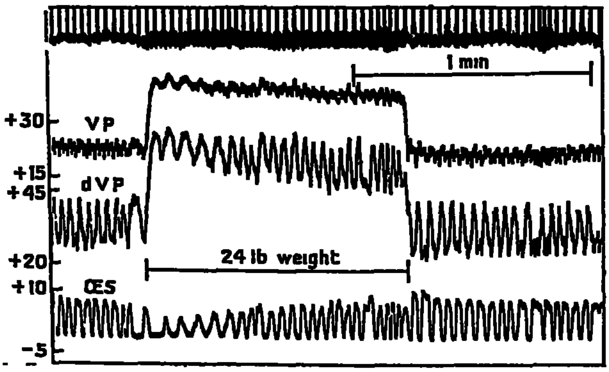

Fig 3—Patient with heart-failure from mitral stenosis Notation as in fig 2 Reference point phlebostatic axis, anteroposterior diameter of chest 16 cm (Artefact restricts troughs of œsophageal record)

The importance of the distinction between filling pressure and central venous pressure is emphasised by the records from a patient with pulmonary valvular stenosis (fig 4) An almost identical rise in central venous pressure was obtained by applying the weight either to the abdomen or to the chest In the first instance filling pressure rose, in the second the rise in central venous pressure was attributable to the rise in intrathoracic pressure, and the filling pressure fell This observation can be repeated at the bedside Most of the patients whose jugular venous pressure rises on the application of pressure to the abdomen show this also if similar compression is applied to the chest, if their breathing continues as normally as possible

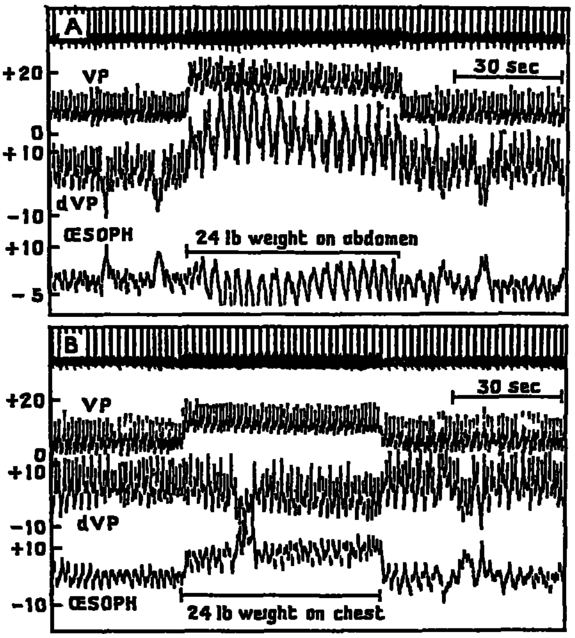

Fig 4—Congenital pulmonary valvular stenosis Notation as in fig 2 Reference point sternoclavicular joint, anteroposterior diameter of chest 18 cm (In B rise in œsophageal pressure, which lasts about 6 sec during application of weight, is due to swallowing and produces negative artefact in differential pressure)

Asthma—In 2 patients with asthma the application of the weight produced no appreciable changes in intrathoracic and central venous pressures In these patients the changes in intrathoracic pressure with breathing was, of course, greater than normal

Discussion

Pressure on the abdomen is one of the standard methods of increasing venous return (Landis and Hortenstine 1950) and is more convenient than exercise, raising the legs, releasing venous occlusion cuffs, while adopting the squatting position or after a Valsalva manœuvre It has, however, numerous disadvantages It is impossible to produce standard pressure with the hand, though Burch (1957) has described a device designed to overcome this objection Even if the pressure is standardised, its effect would be modified by the resistance to the pressure and by differences in the abdominal venous capacity, both in one person on different occasions and between different persons Even if the gross artefact which results from closure of the glottis and a modified Valsalva manœuvre is avoided by asking the patient to continue breathing normally, there is an important variation in the breathing response even in the same person on different occasions The training effect already described might lead the physician to exaggerate the efficacy of his treatment from day to day in a patient with cardiac failure However, patients with cardiac failure, in an attempt to protect the liver from painful pressure, may continue to resist Although one can infer that, if the patient is resisting the hand, it is the descent of the diaphragm which is mainly responsible for the resistance, it is impossible to achieve precision without the simultaneous measurement of at least 6 parameters, which is bound to eliminate the test from clinical practice The test involves a measurement of the jugular and therefore central venous pressure at the bedside, whereas the proper interpretation of the test requires knowledge of the filling pressure—i e, the difference between the pressures within and around the right atrium

Landis and Hortenstine (1950) state "the effects of exercise on venous pressure in normal subjects suggests that the difference between them and patients with overt cardiac failure may be quantitative rather than qualitative" The changes in filling pressure which we recorded during the test lead us to a similar conclusion In addition, the disadvantages already described restrict the value of the test when it is most needed—i e, in detecting early cardiac failure in the absence of other evidence When the reflux, judged by its extent and duration, is clearly abnormal, there is usually more reliable evidence of cardiac failure Some patients had a normal venous pressure after a recent diuresis In such patients a large and sustained increment in venous pressure when the abdomen is compressed may indicate heart-failure

However, when œdema is no longer present, the danger of using a positive hepatojugular reflux to diagnose cardiac failure of which there is no other evidence is emphasised by the findings in the medical student already cited His venous pressure rose 9 cm when a 24 lb weight was applied to his abdomen, and 22 sec elapsed before it returned to its resting level

In patients with severe emphysema abdominal compression raises the intrathoracic pressure This seldom happens in healthy people The simultaneous rise in central venous pressure which results is often taken as evidence of cardiac failure Such an inference is unjustified, because the rise in central venous pressure may be entirely attributable to the rise in intrathoracic pressure which results from the inability of the overexpanded chest to expand further and thereby compensate for the upward displacement of the diaphragm In emphysema a positive hepatojugular reflux may be a more reliable indication that the emphysema is severe than that there is cardiac failure

At present it is by no means universal to measure venous pressure by observation of the internal jugular pulse It is unusual for this to be more than 2–3 cm above the sternal angle in a healthy person In one such person with a venous pressure of 8 cm apprehension appeared to affect the central venous pressure in the same way that it is well known to affect the arterial blood-pressure There is experimental support for the view that apprehension increases venomotor tone (Duggan et al 1953) In our experiments we found that, with practice the clinical method showed good correlation with the direct method described The accuracy of this method largely eliminates the need for the test of hepatojugular reflux

Measurements of the venous pressure from the antecubital vein have shown normal figures to lie between 50 and 140 mm of water above the phlebostatic axis (Winsor and Burch 1946) However, Pedersen (1952) has shown that there is a wide variation in the extent to which the pressure in an antecubital vein is higher than the central venous pressure,

It is a common experience of those who frequently use this method that the venous pressure may be 6 or 7 cm when the external jugular veins are empty, and it is for this reason that this method proves more reliable in practice than the more widely known of Lewis' methods using the external jugular vein, investigated and favourably reviewed by Borst and Molhuysen (1952)

Lewis (1946) concluded that the hepatojugular reflux is "sometimes useful in estimating the amount of blood which is held in the abdomen and in helping to determine the size and position of the cervical veins" Our conclusion is that the only certain value of the manœuvre is in distinguishing a venous from an arterial pulsation in the neck when this is difficult When the internal jugular veins are being used as manometers, it is convenient to be able to raise the column so easily in establishing the normal resting level

Summary and Conclusions

The mechanism of the hepatojugular reflux was investigated in healthy people, in patients with cardiac failure, and in patients with emphysema The prime object was to assess the value of the test as an early sign of cardiac failure

During the test the intra-abdominal pressure rose, and the intrathoracic pressure either rose, remained steady, or fell In most of the patients with emphysema the intrathoracic pressure rose

The filling pressure (the algebraic sum of the intrathoracic and central venous pressures) rose in all the subjects, being highest in those with cardiac failure The variation from the normal was quantitative rather than qualitative The effect on central venous pressure was largely determined by the simultaneous change in intrathoracic pressure Since this was unpredictable, it was concluded that observation of the jugular venous pressure while performing the test of hepatojugular reflux is unreliable as an early sign of cardiac failure In emphysema the intrathoracic pressure response was more predictable and the jugular venous pressure could be expected to rise, but this does not necessarily indicate cardiac failure

The test is of value in identifying venous pulsations in the neck

We are grateful to Dr R W D Turner for his cooperation, Dr E B French and Dr W E Medd for helpful criticism, colleagues, students, and patients who were the subjects under investigation, Mr J A Ramsay, who made the differential manometer, and Miss Norma Millar for technical assistance This research programme has been supported by a grant from the Scottish Hospitals Endowment Research Trust

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DURATION OF NIGHT FEEDING IN INFANCY

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THE length of time that an infant on " demand feeding " requires to be fed at night is an important issue to the mother longing for an undisturbed night's rest

In an attempt to answer this question the eight medical officers* in charge of infant-welfare centres in Area 2 of Middlesex County Council (Southgate, Wood Green, Friern Barnet, and Potters Bar) recorded the birthweight, place of birth, and method and hours of feeding of every infant aged up to about 6 months attending their centres

" Demand feeding " is the accepted method of infant feeding throughout the area and is encouraged by all the medical officers and health visitors at the centres In practice this means that the babies are fed about every three or four hours, but occasionally the intervals may be either shorter or longer according to the baby's demands

Night feeding seems to stop fairly suddenly Typically the baby sleeps through the night two or three times one week and next week or the week after no longer demands night feeds

The mothers say that babies who have never had a night feed have slept through the night from about 10 or 11 P M until about 5 or 6 A M from birth

The end of night feeding was reckoned from the age at which the baby went without one feed at night and so reduced by one the number of feeds it had in twenty-four hours

The survey showed no significant difference between bottle-fed and breast-fed babies or between those born at home and in institutions The important factor was birthweight The accompanying table shows the relation between birthweight and duration of night feeding

(1) In group A 9% and in group D 29% never had a night feed

(2) In group A 27% and in group D 52% had ceased night feeds by the age of 4 weeks

(3) In group A 62% and in group D 81% had ceased night feeds by the age of 2 months

(4) In group A 91% and in group D 89% had ceased night feeds by the age of 3 months

By the age of 3 months the birthweight had ceased to influence the issue

RESULTS OF SURVEY

Group	Birthweight (lb)	No of babies	No night feed	None after 4 weeks	None after 2 mos	None after 3 mos	None after 4 mos	Continued after 4 mos
A	Less than 6½	55	5 (*9*%)	15 (*27*%)	34 (*62*%)	50 (*91*%)	51 (*93*%)	4 (*7*%)
B	6½–7	58	10 (*17*%)	24 (*41*%)	42 (*72*%)	50 (*86*%)	54 (*93*%)	4 (*7*%)
C	7–8	90	24 (*27*%)	45 (*50*%)	66 (*73*%)	80 (*89*%)	83 (*92*%)	7 (*8*%)
D	More than 8	63	18 (*29*%)	33 (*52*%)	51 (*81*%)	56 (*89*%)	59 (*94*%)	4 (*6*%)
	Total	266	57 (*22*%)	117 (*44*%)	193 (*73*%)	236 (*89*%)	247 (*93*%)	19 (*7*%)

I have drawn particular attention to the extreme groups A and D It will be noted that groups B and C are entirely comparable

I wish to thank Dr Kenneth Soddy for his interest and help in the survey The work was undertaken with the consent and approval of Dr W C Harvey, the area medical officer, whom also I wish to thank The Middlesex County Council takes no responsibility for any statements contained in this article

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* Dr L A Crawford, Dr M C Douglas, Dr K I Kerr, Dr N T O'Callaghan, Dr E S Stephen, Dr E M Waterhouse, Dr J White, and Dr J R Campbell

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ALLERGIC SKIN RESPONSES ABOLISHED UNDER TREATMENT OF ASTHMA AND HAYFEVER BY HYPNOSIS

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THE successful relief of symptoms of various allergic conditions by hypnosis has been widely reported (Doswald and Kreibich 1905, Asher 1956, Fry 1957, Kennedy 1957, Stewart 1957), but few details of laboratory control during treatment of this kind have been published We therefore tested a patient's skin reactions to known allergens during the relief of associated allergic symptoms by hypnosis

Case-report

A housewife, aged 27, with one son aged 4 years, complained of asthma and hayfever from May to July yearly, for twelve years Her only previous illnesses were mumps and measles in childhood Her brother had had asthma, and her son had infantile eczema during the first year of life

In March, 1957, the patient described her condition as incapacitating between May and July Prevented during these months from performing most of her normal duties as a housewife and mother, she became for this period of each year a " chronic invalid " subject to prolonged attacks of respiratory distress, which occurred mainly at night and left her nervous and often exhausted from lack of sleep She would spend whole nights sitting up in a chair " gasping for breath " Even if during the daytime she had temporary relief from this severe respiratory embarrassment, she was, during these months, never without a " blocked nose " and " running eyes ", with occasional itching round the eyes and long bouts of uncontrollable sneezing

For ten years she had been unsuccessfully treated for these conditions with unidentified pills and inhalants and ephedrine gr $^1/_2$ three-hourly, which she had taken fairly constantly from May to July every summer

In the spring of 1956, however, in the eleventh year of her complaint, she was investigated for specific allergies by skin testing with the extracts of various common allergens marketed by C L Bencard Ltd In this way she was found to be sensitive to pollens normally present in May, June, and July the equivalent extracts being designated by the manufacturers B2 (grasses), B3 (trees), and B8 (spring flowers) The effects on the patient were said to be due mostly to B2

After these tests, and before the hayfever season of 1956, according to the history kindly supplied by the manufacturers, she was given " specific hyposensitisation treatment," by injection, and there was some relief of symptoms The skin-test reactions during this period are described as persisting, and tested again in six months (in January, 1957) the patient was still fully sensitive It was then suggested by the manufacturers that another course of hyposensitisation was indicated if she were to be helped again after May of that year The patient, however, refused further treatment of this kind and was referred by her doctor for hypnosis

Examination

In March, 1957, she was in good health, with pulse-rate 76, temperature 98°F, and respirations 20 a minute Her blood-pressure was 120/90 mm Hg Her chest tended generally to a barrel shape, with an unduly obtuse costal angle and prominent costal cartilages, but its movements were full On palpation and percussion nothing abnormal was discovered, but expiratory rhonchi were heard on auscultation anteriorly over the 3rd and 4th interspaces on both left and right sides, although no mention of any "asthmatic attack" had been made The heart sounds were normal Examination of the central nervous system revealed nothing abnormal except slight, but equal, exaggeration of both knee-jerks and failure to elicit ankle-jerks and plantar responses on both sides The blood-picture, otherwise normal, showed a raised eosinophil-count of 10% of the total white-cell count

Treatment

During the last part of March and the whole of April the patient attended weekly as an outpatient to prepare for hypnotic treatment of the asthma and hayfever by the induction of increasingly deep hypnotic trances The method of induction used was the therapist's own modification of the Erickson-Wolberg "hypnosis by means of hand levitation" (Wolberg 1948)

The patient was a good hypnotic subject and responded quickly to the various routine suggestions by which deeper trances were achieved By the end of April she could be put into a profound hypnotic trance in two or three minutes after lying down on the couch A week before the usual date for the beginning of the patient's yearly attacks direct hypnotic suggestions were made for the first time about her symptoms She was told that this year she would have neither asthma nor hayfever, the therapist concentrating largely on the symptoms previously described by the patient She was told "This year you will have no difficulty with your breathing, either at night or during the day time" and "This year you will not have a blocked nose, your eyes will not run, there will be no itching round your eyes, and you will not have sneezing attacks" Direct suggestions were also made about her sensitivity to pollens and other substances in the atmosphere, and she was told that now she would no longer respond to their presence with "the symptoms of asthma and hayfever"

It is important to note, however, that at no time was any mention made of the extracts of allergens to which she was known to be sensitive, or of any skin tests, or of the results of any such tests made either during this time or on previous occasions

Result

Such treatment, lasting on each occasion up to thirty minutes, was given weekly from April 29 to July 8, and during the whole of this period the patient remained well and, according to her own account, was for the first time in twelve years at this season completely free from any of the symptoms of either asthma or hayfever After a "cold in the head" contracted during the second week in June, she felt on the night of June 15 that "an attack of asthma might be coming on", and she therefore took ephedrine gr $^{1}/_{2}$ and repeated the dose the next morning No asthma developed, and this was the only pharmacological treatment for her usual complaint taken by the patient in the whole season, during which previously she had constantly taken drugs for eleven years

Experimental Methods and Materials

To test the patient's skin reactions during this treatment, weekly skin tests were made with the commercial extracts of the three allergens to which she was known to be sensitive and a control On each occasion the results were measured in terms of the areas of urticarial reaction in sq mm recorded fifteen minutes after testing

To standardise the area of skin involved in each test an aluminium shield, curved to fit the flexor aspect of the patient's arm, was prepared with four holes, 2 mm in diameter on the inside and countersunk on the outside In the tests a separate hole was used for each extract and the control, and one drop, delivered by a single application of the plastic dipper supplied in each bottle of extract, was placed on the skin revealed by the hole in the shield (about 3 sq mm) Multiple pressure through the drop was then exerted ten times, without scratching, with a sterile hypodermic needle A fresh needle was used for each allergen, and the different test sites were identified on the patient's arm by marking in ink with a ball-point pen, care being taken to avoid the test areas

As a check on the effects of different degrees of pressure with the needle—obviously not fully standardised by this means—a comparison was made between the responses due to very light pressure and actual skin punctures made ten times through drops of the extract B2, to which the patient was known to be most sensitive The results of different degrees of pressure over equal areas, assured by the aluminium shield, were about equal

The control fluid, supplied by the manufacturers as allergically inert, was also tested Ten pricks through this fluid, compared with identical treatment of a dry area, gave exactly the same "triple response" reaction (Lewis 1927) and no urticarial weal of any kind

To record results a length of $1^{1}/_{2}$-in -wide 'Sellotape' was placed over the line of test sites fifteen minutes after testing The outlines of the areas of urticaria were then inked with a ball-point pen on the sellotape, which was afterwards removed

To estimate the area involved in each test response and to make accurate comparisons, the outlines on sellotape were subsequently transferred in the laboratory on to lead foil (taken conveniently from the back of old dental X-ray films) These areas of lead foil were then cut out with scissors and a scalpel, and the resulting pieces were weighed Since 1 sq cm of this foil weighed 36 mg, the area of each urticarial weal could be calculated The uniform thickness of the foil used was checked by weighing equal areas cut at random from different parts, and any variation was estimated to be within the limits of experimental error involved and was not significant

The tests were usually made on the flexor aspect of the patient's left arm, with a preliminary test before treatment on the first occasion on April 29, but after treatment on subsequent occasions up to nine weeks At weeks 4, 5, 8, and 9 unexpected tests were also made on the left leg, the aluminium shield being applied to the medial aspect of the thigh At the 10th week the test was made before treatment, and at the same time blood was taken by venepuncture in order to estimate the Prausnitz-Kustner reaction (Prausnitz and Kustner 1921) in a non-allergic volunteer

Results

At the beginning of the course of treatment the patient responded to the allergens B2, B3, and B8 but not significantly to the control She was most responsive to the extract B2 (grasses), an urticarial weal developing in fifteen minutes to 361 sq mm, compared with 72 sq mm for B3 (trees) and 50 sq mm for B8 (spring flowers) The response to the control on this occasion was 33 sq mm of erythema without any evidence of a true urticarial weal such as attended every response to the allergen extracts

Tested after treatment during the following weeks, however, the reactions on the left arm seemed to reflect the improved condition of the patient's health, the skin responses to all three extracts decreasing steadily each

TABLE I—ALLERGIC SKIN RESPONSES DURING HYPNOTIC TREATMENT SHOWING AREAS OF URTICARIA IN SQ MM

Extract, site of test	Tested before treatment	Tested after treatment and direct suggestion re complaint									Tested before treatment	
	Week											
	1	2	3	4	5	6	7	8	9		10	
B2									Direct suggestion re skin tests			Blood taken for P-K reaction
Left arm	361	73	139	142	55	47	0	0		0	0	
Left leg				622	458			556		0		
B3												
Left arm	72	58	33	0	0	38	0	0		0	0	
Left leg										0		
B8												
Left arm	50	28	25	0	0	28	0	0		0	0	
Left leg				944				611		0		
Control												
Left arm	(33)	(22)	0	0	0	0	0	0		0	0	
Left leg				0				0		0		

week and reaching zero together for the first time after the seventh treatment, but these results did not apply to the occasional unexpected tests on the left leg, which at weeks 4, 5, and 8 gave wide areas of urticarial response, in spite of what was happening to the left arm

At the 9th week, therefore, the procedure was changed and, while the patient was in the hypnotic trance, an additional and direct suggestion was made that, apart from the general improvement in her health, her skin would afterwards be unresponsive to tests with the three extracts anywhere on her body Tested immediately on waking there was no urticarial reaction at all to any of the extracts or the control, on either arm or leg

With the patient now consistently free from both asthma and hayfever, and from any skin responses when tested with the known allergens, an attempt was made to elicit the Prausnitz-Kustner reaction in a non-allergic volunteer At the 10th week of treatment, therefore, the patient was skin-tested before treatment and found to be still completely unresponsive to all three extracts and the control Blood was then taken by venepuncture and serum extracted by centrifuge About 0 1 ml volumes of this serum were then injected intradermally at four points on the flexor aspect of the volunteer's right arm

TABLE II—PRAUSNITZ-KÜSTNER REACTION IN VOLUNTEER

Extract	Prausnitz-Kustner reaction (sq mm.)	
	Left arm	Right arm
B2	0	69
B3	0	36
B8	0	0
Control	0	0

The volunteer was next skin tested on the left arm with the three allergen extracts (B2, B3, and B8) and the control, and readings were taken in the usual way after fifteen minutes There was no reaction At thirty minutes after the intradermal injection of the patient's serum, further skin tests were made over the injection sites on the volunteer's right arm with the same allergen extracts (B2, B3, and B8) and the control Whereas there was now no response to the control or to B8, urticarial weals appeared at the sites of application of B3 (36 sq mm) and B2 (69 sq mm) and remained present for twenty-four hours

These results are shown in tables I and II

Discussion

An allergic causation of the patient's asthma and hayfever had been previously established and, in spite of fairly successful hyposensitisation the year before, she was still sensitive to extracts of the three known allergens She was now treated by direct suggestion under hypnosis, and for the first time in twelve years she was completely free from the symptoms of her yearly illness After each weekly hypnotic treatment during this time she was skin-tested on the left arm with the allergen extracts involved, and the responses to these decreased over 7 weeks to zero

But the left arm—the routine testing site—was apparently associated at a cerebral level with the relief of symptoms, for periodic unexpected tests on the left leg showed no significant change in the urticarial reaction, which was considerable When, however, the direct suggestion was made that the patient's skin everywhere would be unresponsive to the three allergens, there was no response in either arm or leg Nevertheless, with the patient now free from both symptoms and skin reaction, it was still possible to produce the Prausnitz-Kustner reaction in the skin of a volunteer normally insensitive to the allergens

Thus the symptoms of the physical illness had been relieved by psychological treatment, although the patient's blood still contained the serological basis of her previous hypersensitivity in the form of passively transferable antibodies or atopic reagins (Coca and Grove 1925) By direct suggestion under hypnosis, it had been possible to establish an overriding psychic system of control, which could not only keep the patient well, but could also inhibit selectively the allergic or atopic reaction in different parts of her body Although presumably central in origin, this control system, because of its powers of selectivity, might be assumed to act peripherally—possibly at some stage in the local process initiating the *release* of histamine, or other endogenous smooth-muscle stimulants such as acetylcholine or 5-hydroxytryptamine (Lewis 1927, Humphrey and Jaques 1954) Inhibition of tissue *response* to these substances is an alternative explanation In either case, neural rather than humoral communication seems to be implied

Laboratory control thus produced results which supported the general clinical observation that three factors may be involved in the ætiology of asthma and hayfever foreign proteins, sensitised tissues, and a psychogenic factor in no way understood In the present case at least the psychogenic element was further shown to be the most powerful of these three, possibly explaining why psychological treatment in the form of suggestion under hypnosis had provided complete relief from symptoms, where other methods of treatment had proved only partially successful

Summary

A patient with a long history of allergic asthma and hayfever was relieved of her symptoms by hypnotic treatment Weekly skin tests showed her decreasing sensitivity to the known allergens When finally the patient had no symptoms or skin reactions, intradermal injection of her serum into a non-allergic volunteer made it possible to demonstrate the passive transfer of the skin sensitivity to the original allergens (Prausnitz-Kustner reaction)

We wish to thank Dr A. Spencer Paterson for his encouragement and for the facilities granted in the Psychiatric Department of the West London Hospital

References overleaf

AUTOIMMUNISATION IN SUBACUTE THYROIDITIS

ASSOCIATED WITH EVIDENCE OF INFECTION BY MUMPS VIRUS

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M D Lond , M R C P

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Subacute thyroiditis was first described as a clinical entity by de Quervain (1904) The original description was confirmed and amplified by de Quervain and Giordanengo (1936), but subacute thyroiditis has, until the past few years, been considered rare The recent increase in frequency of reported cases is probably partly due to more general recognition of its characteristic symptoms and signs and partly to the use of newer aids to diagnosis such as radioiodine and needle biopsy of the thyroid gland There may also be a true increase in incidence as shown by the reports from the Cleveland Clinic, where 27 cases were diagnosed in 1936–45 and 38 cases in 1946–49 (Crile and Rumsey 1950)

For several years subacute thyroiditis has been suspected to be due to a virus (Crile 1948, Fraser and Harrison 1952), but this remained hypothetical until the mumps virus was incriminated in cases reported from Israel (Eylan et al 1957) A positive complement-fixation test using Lederle mumps viral antigen was found for mumps virus in 10 of 11 cases, in 2 the virus was cultured from the thyroid tissue The findings only applied to that particular outbreak, which coincided with an increased incidence of classical mumps The same virus has been incriminated in the case of subacute thyroiditis reported here, which apparently complicated primary thyrotoxicosis

A further feature was the development of antibodies to extract of human thyroid similar to that recently found by Roitt et al (1956) in Hashimoto's thyroiditis This production of anti-thyroid antibodies is of considerabe theoretical interest in that it was in the present patient a temporary phenomenon which later regressed spontaneously

Methods

Radioiodine studies were made with ^{131}I 15 μC, the amounts taken up by the thyroid gland being determined at 24, 48, and 72 hours

Hæmagglutination-inhibition tests for mumps-virus antibody were made by Dr George Belyavin, of University College Hospital, using Enders strain mumps-virus antigen

The antibody titre of the patient's serum against thyroid hormone was estimated by Dr Deborah Doniach and Dr I M Roitt by a modified Oudin technique using as antigen "purified" thyroglobulin 5 mg per ml Similar tests were made by me using as antigen pooled saline extracts obtained from thyroid glands removed post mortem No significant differences in antibody titre were obtained with the two antigen preparations

Complement-fixation tests were made using as antigen the same saline extract of pooled post-mortem thyroid glands 0 25 ml of the patient's serum was inactivated and incubated at 37°C for half an hour with 0 25 ml of antigen and three hæmolytic doses of guinea-pig complement 0 25 ml of a hæmolytic system containing 3% sensitised sheep cells was added, and the tubes were examined for lysis after a further hour's incubation at 37°C Both the antigen and the serum were put up in several dilutions

The serum-gammaglobulin was estimated by paper electrophoresis (Hardwicke 1954)

Case-report

A housewife, aged 43, was first thought to be unwell in March, 1956, by her family, who observed restlessness and prominent eyes In June, 1956, she began to feel ill and to lose weight and noticed that her eyes had become sore and seemed to protrude She became emotionally more labile and subject to mild depression In mid-October, 12 days before admission, stiffness and soreness of her neck muscles developed, and a transient rash appeared on her chin Her throat became sore, and she became increasingly pyrexial, her illness then being diagnosed as primary thyrotoxicosis complicated by pharyngitis Despite treatment with aspirin and sulphadiazine the malaise, pyrexia, and soreness of her throat and neck muscles increased, and she was admitted on Oct 24, 1956, having lost 28 lb in weight in 6 months She had not had any abdominal pain or tenderness or swelling of her salivary glands

Previous history—She had undergone tonsillectomy at the ages of 4 years and 12 years She had never had mumps There had been an increased incidence of mumps in the local schools over the 6 months before her admission to hospital

Family history—There was no recent infectious fever in the family Her two children, aged 10 years and 13, had had classical mumps several years previously A brother with primary hypothyroidism had been maintained on thyroid extract since infancy No anti-thyroid antibodies were found in his serum by the precipitin technique or the tanned red-cell agglutination technique (D Doniach, personal communication)

On examination the patient looked ill and was restless and agitated Her skin was hot and moist She had pyrexia (99°–102°F) and tachycardia (120), obvious eyelid retraction, some exopthalmos, and a fine tremor of her outstretched hands Her pharynx was not inflamed She had a flush over the lower part of her neck and extending to the upper part of her chest, and her skin was warm and hyperæmic Her thyroid gland was tender, both lobes being enlarged, the left more than the right, and the gland felt tense and locally adherent It was estimated to be about twice the normal size No thyroid bruit was audible A small firm non-tender lymph-node lay above the thyroid isthmus, and there were also several small nodes in the posterior triangles of the neck There were no other abnormal signs

Treatment and progress—The patient received no specific treatment apart from mild sedation and intramuscular soluble penicillin G 1,000,000 units twice daily for three days Her malaise rapidly decreased and her temperature and pulse-rate fell to normal within a week Her thyroid gland became less tender and less tense though it was still enlarged Initially the left lobe had been the more affected, but, as this lobe improved, the right lobe became larger and more tender

Initial investigations—Hb 11 9 g per 100 ml , white cells 7000 cm (normal differential count), erythrocyte-sedimentation rate 24 mm in 1st hour (Wintrobe) Chest radiography was normal except for slight lateral compression of the trachea There was moderate proteinuria for the first three days, but the urinary sediment was normal The uptake of radioiodine on the 8th day was 2 7% at 24 hours, decreasing to 1 2% at 48 hours The basal metabolic rate on Nov 8, 1956, 10 days after the remission of pyrexia was −16%

Autoimmunisation—Circulating antibodies to human thyroid extract were found on Nov 11, 1956, at titre of 1 2 of serum

Evidence of mumps infection—A positive hæmagglutination-inhibition test for mumps virus was found to a titre of 1 320 of serum on Nov 11, 1956, decreasing to 1 80 after 26 days, and to 1 40 after a further 31 days

Thyroid biopsy—Biopsy of the isthmus (Mr V Brookes) on Nov 5, 1956, showed that the thyroid gland was bound to

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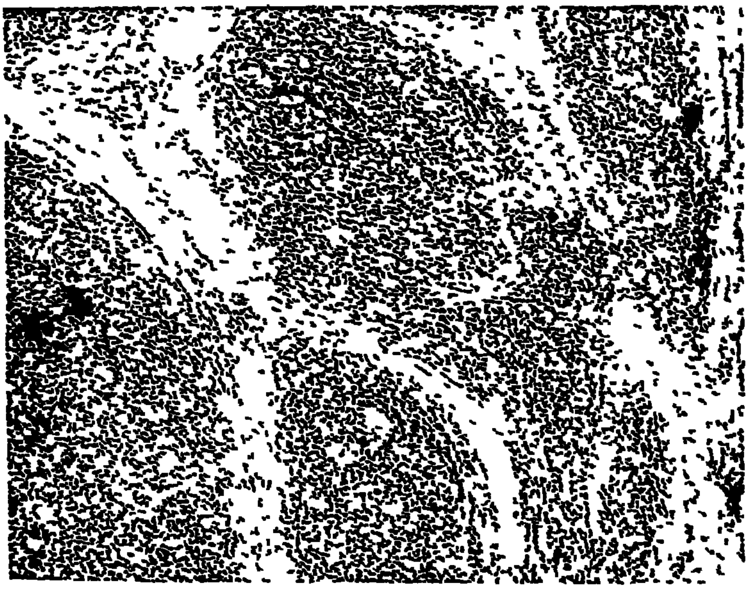

Fig 1—Section of thyroid gland showing interlacing bands of acellular fibrous tissue surrounding areas of surviving parenchyma with heavy cellular infiltration (Hæmatoxylin and eosin. ×30)

the surrounding tissues by adhesions, but not to the extent usually seen in Riedel's chronic thyroiditis The gland felt hard, its surface irregular, and the cut surface extremely firm Histological examination (Dr D B Brewer) showed (figs 1 and 2) the thyroid divided up into demarcated lobules by bands of dense acellular fibrous tissue The lobules, in contrast to these bands of fibrous tissue, were very cellular and consisted of small acini closely applied to one another The outlines of the acini were obscured by a heavy cellular infiltration which was both intra-acinar and interacinar The cells consisted of polymorphs, lymphocytes, and plasma cells, but large intra-acinar giant cells were also present No lymphoid follicles were seen The picture was that of a fairly chronic stage of giant-cell thyroiditis

Further progress—The patient was symptom-free on discharge Her thyroid gland was slightly tender, the right lobe being enlarged and the whole gland easily palpable because of its firm consistence The surrounding lymph-nodes had become smaller Slight exophthalmos and lid retraction were still present Serial studies were made of the clinical state and thyroid function, *and of the changing titre of antibodies to thyroid* extract over the following 11 months (table and fig 3) The patient began to put on weight, and clinical evidence of thyrotoxicosis disappeared except slight lid retraction The thyroid gland remained firm, with a slightly enlarged right lobe The circulating thyroid antibody titre increased over 3 months to 1 16 and then decreased progressively to 1 4 The antibodies were also demonstrated by complement fixation to a titre of 1 40 on Jan 1, 1957, and to a titre of 1 30 on March 21, 1957 Serial serum flocculation tests showed an abnormality which could be correlated with the level of the serum gamma-globulin and the titre of anti-thyroid antibodies (see table) The uptake of radioiodine increased slowly but steadily from 2 7% in 24 hours on admission to 57 9% in 24 hours on Sept 18, 1957 The turnover remained rapid, and on Sept 18, 1957, the uptake in 72 hours had decreased to only 38%, equivalent to a half-life of 3 7 days The basal metabolic rate fell to normal after 3 weeks and has since remained in the normal range, though showing a tendency towards increase (table and fig 3)

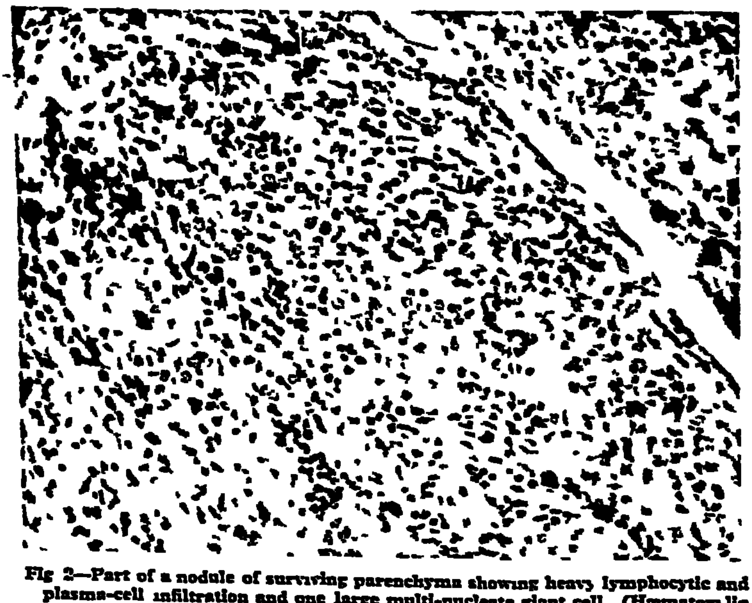

Fig 2—Part of a nodule of surviving parenchyma showing heavy lymphocytic and plasma-cell infiltration and one large multi-nucleate giant cell. (Hæmatoxylin and eosin. ×200)

RELATIONSHIP OF TITRE OF ANTI-THYROGLOBULIN ANTIBODY TO SERUM GAMMAGLOBULIN, FLOCCULATION TESTS, AND UPTAKE OF RADIOIODINE DURING COURSE OF ILLNESS

Date	Thyroglobulin precipitin titre	Gamma globulin (g per 100 ml)	Flocculation tests (units)		% radioiodine uptake at		
			Thymol turbidity	Zinc sulphate turbidity	24 hr	48 hr	72 hr
Nov 1, 1956	—	—	—	—	2 7	1 2	—
„ 11 „	1 2	—	2	7	15 9	—	—
Dec. 5 „	1 4	1 6	2	11	18 1	16 7	—
Jan 5, 1957	1 16	2 2	7	18	31 0	20 0	14 1
Feb 5 „	—	—	—	—	39 1	—	22 5
Mar 21 „	1 8	2 2	4	14	—	—	—
April 25 „	—	—	—	—	47 0	—	29 8
May 24 „	1 4	1 9	—	—	—	—	—
Sept. 18 „	1 4 (weak)	1 5	3	7	57 9	—	38·0

Discussion

Diagnosis of Subacute Thyroiditis

The subacute thyroiditis followed a typical course in this patient, with a gradual onset, when pharyngitis was suspected, and later the development of toxæmia, high pyrexia and tenderness of the thyroid gland The tendency for the thyroiditis to affect one lobe and then to subside slowly there but to flare up in the other lobe is well recognised and has led to the name "creeping thyroiditis" Crile and Rumsey (1950) have found that, when the pain, swelling, and tenderness are still confined to one lobe, the uptake of radioiodine may be much depressed, showing that the whole gland is involved

Thyrotoxic symptoms are often present during the acute stage, but the malaise and toxæmia are usually more severe than the degree of thyrotoxicosis would lead one to expect. The duration of subacute thyroiditis has varied in different series, though cases have been reported in which the thyroid gland was tender for more than

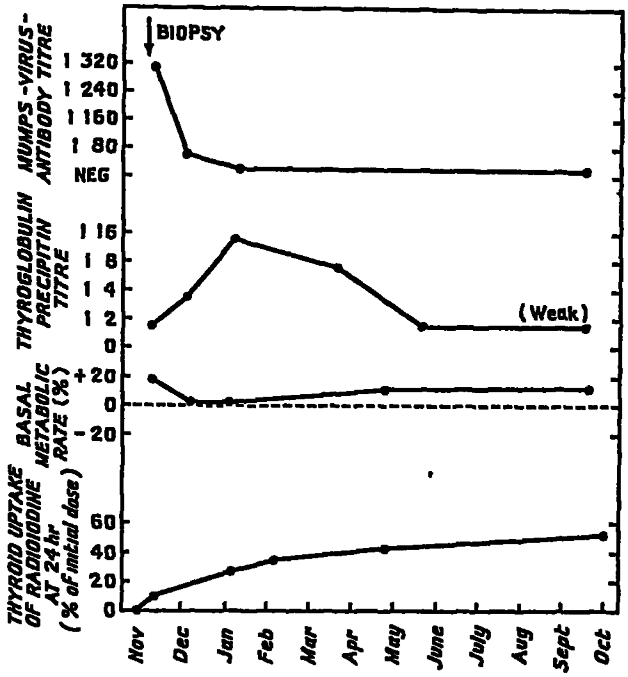

Fig 3—Changes in basal metabolic rate, % radioiodine uptake at 24 hours, titre of mumps-virus antibody, and titre of anti-thyroglobulin precipitin from onset of subacute thyroiditis

a year (Lindsay and Dailey 1954, Stalker and Walther 1951), the duration of acute tenderness for about $2^1/_2$ weeks followed by its gradual decrease over a further 6 weeks, as in the present case, is more usual The clinical diagnosis in this case was confirmed by the histological appearances in the biopsy specimen

Thyrotoxicosis and Thyroiditis

The patient had symptoms and signs of hyperthyroidism for at least 7 months before the acute phase, this suggests primary thyrotoxicosis rather than the insidious onset of thyrotoxic symptoms due to thyroiditis The radioiodine studies after recovery point to a return of this hyperthyroidism Subacute thyroiditis has been followed by thyrotoxicosis within weeks or months on several occasions (Sheets 1955, Perloff 1956), but the history of preceding thyrotoxic symptoms makes it unnecessary to invoke this explanation in the present case Most patients have normal thyroid function after subacute thyroiditis 10 patients followed by Eylan et al (1957) became euthyroid, with a normal uptake of radioiodine, within 6 months and remained euthyroid, this series is particularly valuable for comparison because the thyroiditis was proved to be associated with mumps infection Despite the large number of cases of thyroiditis published to date an association with pre-existing thyrotoxicosis has not been traced Lindsay and Dailey (1954) found no association with any pre-existing disease of the thyroid gland, but Volpe and Johnston (1957) reported 6 cases which followed a simple non-toxic goitre

Evidence for Mumps as Causal Agent

The high level of mumps-virus antibody found by Dr Belyavin during the acute stage of thyroiditis and the fall in titre over the next few months suggested that the thyroiditis was due to mumps virus The possibility of an anamnestic increase in complement-fixing antibody was investigated by Eylan et al (1957) when they first reported their epidemic of subacute thyroiditis, but no such increase was found in other acute fevers The hæmagglutination-inhibition tests made in the present case are probably a more specific index of mumps infection than is the test with complement-fixing antigens, and strongly suggest that the patient had active mumps at the time of the thyroiditis The increased incidence of classical mumps in the local schools over the 6 months before the acute thyroid symptoms is of interest

Autoimmunisation and Thyroid Gland

The finding of antibodies to "purified" human thyroglobulin (less than 95% pure) in many cases of Hashimoto's thyroiditis by Roitt et al (1956) has helped to clarify our understanding of the pathological pattern in that disease and has provided a valuable stimulus to investigators of other types of thyroiditis

The precipitin technique is at present the most valuable method of detecting the antibody but it is not very sensitive The agglutination of tanned red cells coated with antigen, a method used by Prof E Witebsky, is extremely sensitive but more difficult and laborious Complement-fixation tests have not yet been fully assessed Complement-fixing antibodies have been found in most cases of Hashimoto's thyroiditis, many cases of spontaneous myxœdema, occasionally in thyrotoxicosis, and rarely in healthy people

Anderson et al (1957) have followed up these positive complement-fixation tests in apparently "normal" hospital inpatients by post-mortem examination of the thyroid gland where possible, and observed changes which appear similar to, but less pronounced than, the changes of Hashimoto's disease, with lymphocytic infiltration, formation of lymph follicles, and loss of many thyroid acini

The finding by Anderson et al (1957) of histological abnormalities in the thyroid glands of "normal" patients with positive complement-fixation tests is of particular interest in view of Thomson's (1957) work on thyroid histology He found areas suggesting an "immunological reaction pattern" in operation specimens of sporadic goitre, thyrotoxic thyroid glands, and one carcinomatous thyroid gland Various insults to the thyroid gland seem able to cause damage to the acini and to release thyroglobulin Probably infection by mumps virus was the insult in the present case, and it is reasonable to wonder whether the severe infiltration by lymphocytes and plasma cells may be a further indication of antibody production and of local immune reaction Possibly some cases of Hashimoto's thyroiditis may have a similar precipitating cause, and the search for viral infection will doubtless be intensified in the future

Transcience of Autoimmunity

The Lancet (1957) suggests that the antigen-antibody reaction once initiated might become self-perpetuating, but the present case shows that this is not inevitable The titre of antibody decreased although the patient was clinically euthyroid with an increasing uptake of radioiodine by his thyroid gland This suggests that the leak of thyroglobulin had been stopped, and possibly indicates that the viral infection was no longer damaging the acina epithelium—a finding which would fit in with the decreasing titre of mumps-virus antibody It is fascinating to speculate whether total destruction of the thyroid gland and consequent myxœdema, as in Hashimoto's thyroiditis, could occur in thyroid glands with smaller residual powers of recuperation The incidence of a complicating autoimmunisation in subacute thyroiditis is unknown We have examined 3 further cases of subacute thyroiditis with a positive mumps-virus hæmagglutination test

In 1 a weak antibody titre (1 2) to thyroid extract was found 2 months after the onset of thyroid enlargement, this case is of particular interest because of the absence of thyroid tenderness, the only subjective symptom being slight aching in the neck radiating to below the right ear The uptake of radioiodine was 36% of the total dose at 24 hours despite clinical evidence of thyrotoxicity and a basal metabolic rate of +49%

The 2 other cases were seen 6 and 8 months after the acute stage, no antibodies were detected by the precipitin technique

In the 56 patients described by Volpe and Johnston (1957) no residual permanent hypothyroidism was found, suggesting that if autoimmunisation has developed it had not caused progressive damage to the thyroid gland

Summary

A case of subacute thyroiditis is described which apparently complicated primary thyrotoxicosis

A positive hæmagglutination-inhibition test for mumps-virus antibody in a high titre during the acute stage and decreasing later suggested that the thyroiditis was due to mumps virus

Autoimmunisation to "purified" human thyroglobulin took place after the acute stage and reached a peak 3 months later, after which the amount of circulating antibody gradually decreased

I wish to thank Dr C F Hawkins for permission to publish, Prof J R Squire for much valuable advice and facilities for immunological work, Mr W H Bond for the radioiodine studies, Dr D B Brewer for help with the histology, Dr G Belyavin for permission to use his figures on mumps viral antibody titres, and Dr D Doniach, of the Middlesex Hospital Institute for Clinical Research, London, for the initial immunological investigations and much valuable information

ADDENDUM

This patient is mentioned by I M Roitt and D Doniach in a table about thyroglobulin precipitin reactions in other thyroid diseases (*Proc R Soc Med* 1957, 50, 960) Further follow-up studies in February, 1958, show that antithyroid antibodies are now detectable only in undiluted serum

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"Dr Wilks said he could not speak too strongly in denunciation of the old fashion, the plan of treating hysteria by physic instead of by moral [psychotherapeutic] means, a plan which was known to be useless, and was yet followed as a matter of routine He had, he said, often reflected with surprise upon a remark made by so intelligent a man as the late Dr James Johnson, who, when called to visit a girl who had been in bed with various hysterical affections for five years, and who had been drenched with gallons of physic, inquired if every 'stinking thing' in the Pharmacopœia had been given her, and when answered in the affirmative, declared he could do no more"—Sir Samuel Wilks *Lectures on Diseases of the Nervous System* 2nd ed London, 1883, p 464

INTERMITTENT HYPERPARATHYROIDISM

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HYPERPARATHYROIDISM should be suspected in any patient with recurrent renal calculi (Albright and Reifenstein 1948, Richardson 1953) This article describes a patient with such a history, and from whom a parathyroid adenoma was subsequently removed, the preoperative biochemical results showed that the adenoma was only intermittently overactive

Case-report

A woman, aged 50, attended the outpatient department in April, 1956, having had an attack of renal colic 5 days previously, she had no other urinary symptoms In 1946 she first had left-sided renal colic, this recurred on and off till 1948, when a left pyelolithotomy was performed In 1951 she underwent left nephrectomy because of stones, and in 1953 she had a right pyelolithotomy

There were no abnormal physical signs on examination, her blood-pressure was 120/80 mm Hg An intravenous pyelogram (I V P) showed compensatory hyperplasia of the right renal outline excretion was first seen at 5 minutes, and there was dilatation of the calyceal system, in the lower minor calyx there was a moderate-sized calculus and several minute calculi The urine was sterile on culture

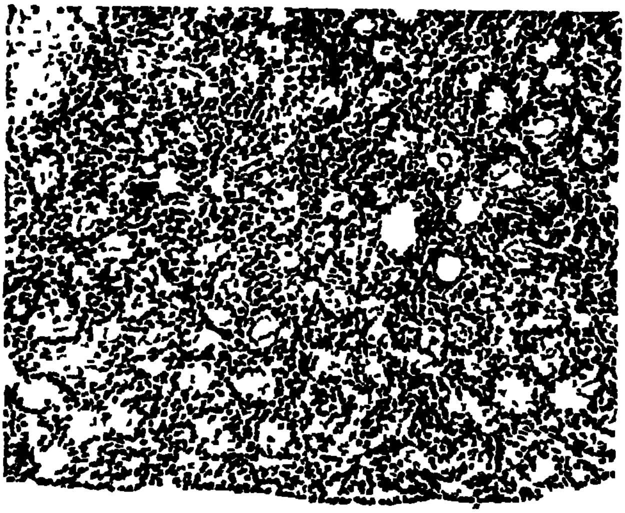
She was admitted to hospital on Sept 7 under the care of Mr C J B Murray, for investigations before the removal of the renal calculus She had had no more attacks of colic An I V P showed that the main calculus had become larger Her hæmoglobin was 74% packed-cell volume 35%, erythrocyte-sedimentation rate (E S R.) (Wintrobe) 10 mm in the first hour, and leucocyte-count 6400 per c mm with a normal differential count The results of biochemical tests are given below

On Sept 30 she had another attack of renal colic, and metabolic investigations were interrupted A retrograde pyelogram on Oct 2 showed that the right renal pelvis contained 60 ml urine, and that the large renal calculus had moved to the upper part of the ureter On Oct 5 Mr E W Riches performed a right pyelolithotomy and partial nephrectomy, the lower pole of the kidney was amputated because it was known to contain minute calculi, one of which could be felt but not dislodged at operation After operation the patient was anuric until Oct 10 (blood-urea 141 mg per 100 ml) During the anuric phase she was treated partly by intragastric drip and partly by intravenous fluids Urine started to drain on Oct. 10, and a urinary fistula developed on Oct 11, the fistula had closed spontaneously by Oct 17 At no time during the anuric or diuretic phases were the patient's serum-electrolyte levels seriously deranged, and they had returned to normal limits by Oct 17

Histological examination of the kidney revealed active chronic inflammatory changes in the calyces with increased submucous fibrosis, and focal inflammatory areas in the renal parenchyma in which there were scanty spherical deposits of calcium

Biochemical tests were resumed at the end of October, and further tests were made when she was readmitted to hospital in November after a period of convalescence The results of these tests are presented in the next section

Mr C J B Murray explored the patient's neck on Nov 28 The biochemical data did not allow of a firm preoperative diagnosis of hyperparathyroidism, and there was no X-ray evidence to suggest the diagnosis, many alternative diagnoses had, however, been excluded, such as sarcoidosis and multiple myeloma At operation the left and right superior parathyroid glands were removed, the left gland was bilobed, measuring 2 × 1 2 × 1 2 cm , and the right was approximately spherical (diameter, 0 6 cm) Her postoperative course was uneventful, with only mild temporary asymptomatic hypocalcæmia



Periphery of the parathyroid adenoma, both clear cells and oxyphil cells are visible (× 120)

Sections of the left superior parathyroid gland showed replacement by an encapsulated adenoma composed of both clear and oxyphil cells, the proportions of the cellular components varied in different areas, and the clear cells tended to be arranged in an alveolar pattern (see fig), the tumour cells were regular in configuration and there was no histological evidence of malignancy The right superior parathyroid gland was histologically normal

The patient was discharged on Dec 7, and an I V P on Dec 28 showed that the right kidney was excreting well She was last seen on Oct 11, 1957, at that time her blood-pressure was 130/80 mm Hg, and a plain radiograph of her abdomen did not reveal any renal calculi

RESULTS OF BIOCHEMICAL INVESTIGATIONS

Period	Date	Blood-urea (mg per 100 ml)	Serum-calcium (mg per 100 ml)	Plasma phosphate (mg per 100 ml)	Urine volume (ml per 24 hr)	Calcium excretion in urine (mg per 24 hr)	Mean urinary calcium concentration (mg per 100 ml)
1	1956 Sept 7	33					
	„ 12		12 4				
	„ 21		12 0	1 4	1290	265	20 5
	Oct 4	40					
2	Oct 17	57					
	„ 28				1495	275	18 4
	„ 29	29 (F)	9 8 (F)	2 1 (F)	2500	482	19 3
3	Nov 21		11 4 (F)	2 9 (F)	2100	225	10 7
	„ 22	38		3 5			
	„ 23				2320	258	11 1
	„ 24				2400	298	12 4
	„ 26		12 2 (F)	2 1 (F)	2290	273	11 9
	„ 27				2145	272	12 6
4	Dec 4		10 0		1810	120	6 6
	1957 Mar 1	39	9 8	2 3			
	Oct 11	27	9 3	2 9			

The table is divided by horizontal lines into four subsections

1 Before pyelolithotomy and partial nephrectomy (performed Oct 5, 1956)
2 After recovery from the anuric episode
3 *Before parathyroidectomy (performed Nov 28, 1956)*
4 After parathyroidectomy

The blood samples were not all taken at the same time of day Figures with F in parenthesis were obtained on samples taken at 8 A M , after the patient had fasted overnight, other blood samples in hospital were taken 2 hours after breakfast

Urine collections were begun at 8 A M *on the dates indicated and* continued for 24 hours The urinary calcium concentrations are overall average figures for each 24-hour period

A calcium-infusion test was performed on Oct 29 1956, the infusion started at 9 A M

Biochemical Investigations

Calcium in serum and urine was estimated by the method of Kramer and Tisdall (1921, 1923) Inorganic phosphate in plasma and urine was estimated by the method of Kuttner and Lichtenstein (1930)

The normal range for serum-calcium is 9–11 mg and for plasma-phosphate 2 5–4 5 mg per 100 ml The normal urinary excretion of calcium is found to be 100–300 mg per 24 hours at this hospital (see also Nabarro 1954), Dent and Hodson (1954) give 120–220 mg per 24 hours as the normal range of urinary calcium excretion, whereas Pyrah (1956) accepts up to 350 mg per 24 hours as normal The normal urinary excretion of phosphorus is 0 5–1 5 g per 24 hours

Many of the results are collected in the accompanying table, which is divided by horizontal lines to correspond with the following four subsections

1 *September, 1956 before pyelolithotomy and partial nephrectomy* —A diagnosis of hyperparathyroidism was indicated by the observation of raised serum-calcium and lowered plasma-phosphate levels However, the urinary calcium excretion on an ordinary diet was 265 mg per 24 hours and, after equilibration on a diet containing 120 mg of calcium per 24 hours, the urinary calcium excretion fell to 159 mg per 24 hours Both of these results are within normal limits (Nabarro 1954), though Pyrah (1956) holds that on a low calcium intake a daily urinary calcium excretion of 150–200 mg per 24 hours is suggestive of hyperparathyroidism The urinary phosphorus excretion was 486 mg per 24 hours and the serum-alkaline-phosphatase was 6 6 King-Armstrong (K-A) units per 100 ml At this time the blood-urea was normal

2 *October, 1956 after recovery from the anuric episode* —On Oct 29 a calcium-infusion test was performed (Howard et al 1953), the load of intravenous calcium was 20 mg per kg body-weight On that day the blood-urea was 29 mg per 100 ml , and the serum-electrolytes were sodium 139, potassium 4 1, chloride 99, alkali reserve 27 mEq per litre *(all within normal limits)*

In the control period before the infusion the patient passed 1495 ml of urine, containing 275 mg of calcium and 482 mg of phosphorus, in the test period these figures were 2500 ml , 482 mg , and 283 mg respectively At the start of the infusion the serum-calcium was 9 8 mg and the plasma-phosphate was 2 1 mg per 100 ml At the end of the infusion the plasma-phosphate was 2 5 mg per 100 ml , and it continued to rise, to 2 9 and 3 4 mg (±0 1 mg) at 4 and 8 hours respectively after the end of the infusion The patient vomited once (150 ml) soon after the *infusion ceased The response to this test was* similar to that described by Howard et al (1953) for normal people

The results of tests in this subsection indicated that the patient's metabolism of calcium and phosphorus was normal, the most significant of these normal results was the serum-calcium of 9 8 mg per 100 ml , supporting evidence being provided by the urinary calcium excretion before the infusion of calcium and by the response to the infusion

3 *November, 1956 before parathyroidectomy* —The results in this subsection are similar to those in subsection I

The serum-calcium had returned to abnormally high levels, and one of the three plasma-phosphate levels was subnormal The urinary calcium excretion ranged from 225–298 mg per 24 hours (mean 265 mg) and the serum-alkaline-phosphatase was 8 K-A units per 100 ml

The *total serum-protein* was 6 4 g per 100 ml (albumin 3 8 g per 100 ml and a normal electrophoretic pattern) The E.S R (Westergren) was 7 mm in the first hour

4 *After parathyroidectomy* —The serum-calcium returned to normal and has remained normal After operation, the daily urinary calcium excretion fell markedly, but it has not been redetermined since discharge from hospital *The plasma-*phosphate was subnormal on March 1, 1957, but was normal on Oct 11 On March 1 the serum-alkaline-phosphatase was 6 6 K-A units per 100 ml

Discussion

Although this patient now only has part of one kidney remaining, her prognosis as far as the recurrence of renal calculi is concerned has been greatly improved The most important effect of parathyroidectomy was to reduce the urinary calcium excretion from 266 mg to 120 mg in 24 hours

The last column in the table shows the urinary calcium concentration, an important determination in patients who have a tendency to form renal calculi The maximum concentration of which a patient is capable can be determined during a calcium-infusion test, it probably shows considerable individual variation (some of Richardson's (1953) patients excreted urine containing 28 mg of calcium per 100 ml without being subjected to a calcium infusion), but, for this patient, the maximum urinary calcium concentration was about 20 mg per 100 ml By increasing her fluid intake (November, 1956) this patient considerably reduced her urinary calcium concentration, and further reduction followed parathyroidectomy

Before parathyroidectomy the biochemical results fell into three clear subdivisions, corresponding to the first three (horizontal) subdivisions in the table In September and November, 1956, hyperparathyroidism was indicated by hypercalcæmia and, on two occasions by hypophosphatæmia Urinary studies did not support the diagnosis, though in retrospect the average urinary calcium excretion of 266 mg per 24 hours should probably have been regarded as abnormal (cf Dent and Hodson 1954), as should the urinary excretion of 159 mg of calcium per 24 hours, after stabilisation on a dietary intake of 120 mg of calcium per 24 hours (Pyrah 1956, McGeown and Bull 1957) By contrast, the results on Oct 28–29, 1956, were strikingly normal, with normocalcæmia and a urinary calcium excretion of 275 mg in 24 hours (which was at that time considered to be normal), followed by a normal response to the calcium infusion test

This pattern of results is most readily explained by the hypothesis that the parathyroid adenoma was only intermittently overactive, being inactive at the end of October, 1956 Such a possibility was suggested by Richardson (1953), though none of his cases demonstrated intermittent overactivity clearly Intermittent hypercalcæmia is mentioned as a pitfall in the diagnosis of hyperparathyroidism by Fraser and King (1957), when discussing why a patient should simultaneously have normocalcæmia, hypophosphatæmia, and hypercalciuria, this triad was shown by this patient in the control period before the calcium infusion (regarding 275 mg of calcium per 24 hours as an abnormally high urinary excretion) The two other possible explanations discussed by Fraser and King for this biochemical triad were induced acidosis (Shohl 1939, Farquharson et al 1931), and idiopathic hypercalciuria (Albright et al 1953), on Oct 29, 1956, the patient's acid-base balance was normal, and she clearly did not have idiopathic hypercalciuria When hypercalciuria and hypophosphatæmia are observed in a patient with normocalcæmia who is not acidotic, Fraser and King (1957) advocate the taking of serial blood samples so as to avoid missing a latent hypercalcæmia

It is impossible to say whether the period of inactivity of this patient's adenoma was spontaneous, or precipitated by the complications that followed pyelolithotomy and partial nephrectomy This case-report, however, shows that the serum-calcium level can fluctuate widely in a patient with hyperparathyroidism, and it shows that, in the absence of other unequivocal evidence of hyperparathyroidism, such fluctuations can endanger the diagnosis

The plasma-phosphate level was subnormal on Oct 29, 1956, and this was the only biochemical test then that indicated a diagnosis of hyperparathyroidism, considering the overall results for that period by themselves It emphasises the value of determining the plasma-phosphate level in routine screening of patients for suspected hyperparathyroidism Hypercalcæmia may be only intermittent, and the observation of a low plasma-phosphate level during a normoclacæmic interval may then be particularly important

Summary

A case is reported of hyperparathyroidism due to an adenoma that was only intermittently overactive Difficulties arise in the diagnosis of intermittent hyperparathyroidism, and plasma-phosphate determinations are valuable in such patients

I am very grateful to Mr C J B Murray for permission to publish this case, and I am much indebted to Dr J D N Nabarro and Mr R T Turner-Warwick for many helpful discussions The histological reports and microphotograph of the parathyroid adenoma were kindly supplied by Dr A D Thomson, and I should like to thank the staff of the Courtauld Institute for the biochemical estimations

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TRIPELENNAMINE (PYRIBENZAMINE) IDIOSYNCRASY

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BECAUSE tripelennamine ('Pyribenzamine') is one of the constituents of a popular anti-histamine preparation commonly prescribed in this country, it is considered that the case reported here may assist in the elucidation of similar diagnostic puzzles Although such cases must be rare, the symptoms are severe, and failure to recognise the condition could lead to tragedy

Case-report

A married woman, aged 49, was admitted to hospital on April 25, 1957, in coma Five days earlier she had complained of suddenly feeling cold, nausea, and then diarrhœa. Since then she had become progressively worse, complaining of pains in her joints and back, severe headache, and loss of appetite A dry unproductive cough and a low pyrexia (100°F) appeared, abdominal pains became severe, and the patient began to ramble mentally

On admission signs of dehydration were evident, and her reflexes were sluggish, but her pupils reacted to light She could not be roused

Treatment and progress —An intravenous saline drip was given, and over the next twelve hours her general condition improved and sphincter control was regained Twenty-four hours after admission she was conscious but confused and disoriented in place and time She took fluids willingly and her diarrhœa abated She had photophobia and severe tenderness over the lower edge of her liver and gall-bladder Clinical, radiological, and laboratory investigations were undertaken to exclude conditions such as acute cholecystitis, infective hepatitis, renal disease, and infection by salmonella All the findings were normal except a relative neutropenia of 6000 white blood-cells per c mm On the third day urticaria appeared on the scalp, arms, and feet and was controlled with 'Antistin' 50 mg four-hourly and promethazine 25 mg at night In spite of help and advice from colleagues no satisfactory diagnosis was made before the patient was discharged after eleven days in hospital

Later developments —Ten days after discharge from hospital the patient was again seen, because the urticaria had recurred severely Chlorpheniramine ('Piriton') was prescribed Late that evening the patient's husband telephoned to say that the nausea, vomiting, and disorientation had returned The patient, unable to obtain piriton immediately, had taken a tablet of tripelennamine-antistin mixture The symptoms began some two hours after ingestion of the tablet It was then learnt that she had been given these tablets, ten days before the onset of the original symptoms, by a surgeon who was treating her chronic rhinitis Subsequently piriton gave the required relief for both the urticaria and the rhinitis without ill effect

Discussion

A previous history of infantile eczema, hay-fever, urticaria, allergic rhinitis, and severe reactions to parenteral and topical administration of penicillin was given The patient had no clear memory of events from the time she was compelled to take to her bed until about twenty-four hours after admission to hospital

In view of the dramatic revelation of the correct diagnosis it was not considered wise to confirm it by further trials of the suspected anti-histamine Antistin had already been given unsuspectingly in hospital, without ill effect, hence tripelennamine remained the likely offender Published reports strengthen this suspicion

Most of the reports of toxic effects from tripelennamine were published in America several years ago, but *The Lancet* (1950) called attention to the dangers of overdosage with anti-histamines Wyngaarden and Seevers (1951) and Sparling (1951) were mainly concerned with the toxic effects of overdosage with tripelennamine and diphenhydramine ('Benadryl') in children That severe toxic reaction does not depend entirely on dosage was noted by Judge and Dumars (1953) and Bunce and Huntley (1953), the former reported delirium, coma, confusion, headaches, and pyrexia among the toxic effects Lott et al (1948) mentioned disorientation, dryness of the mouth, and diarrhœa, and Loveless (1947) shock, urticaria, and neutropenia Judge et al also stated that toxic reactions were commoner in persons with a previous history of allergy They noted that the reactions appeared from two to eight hours after absorption of the drug

Summary

A case of idiosyncrasy to tripelennamine, distinct from toxic effects due to overdosage, is presented

There were severe neurological and gastrointestinal symptoms, with allergic skin reactions

I am indebted to Air Marshal Sir P B Lee Potter, director general of medical services, and Dr R D Darley, of Esher, Surrey, for permission to publish this case, and to Squadron-Leader J S N Mitchell, of the Royal Air Force Hospital, Uxbridge, for the clinical details

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HÆMORRHAGIC DIATHESIS DUE TO INCREASED CAPILLARY FRAGILITY SECONDARY TO OVARIAN DEFICIENCY

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THE vascular changes associated with menstruation are probably not entirely confined to the endometrium The fragility of the skin capillaries has been shown to be increased just before each menstrual period and during its first few days (Bickel 1931, Schultzer 1934, Salvatore 1952, Buchholz 1953), and women certainly bruise more easily at these times (Goldburgh and Gouley 1940) A contributory factor may sometimes be premenstrual thrombocytopenia, and cases have been described of thrombocytopenic purpura associated with menstruation (Nagy 1925, Minot 1936)

Some workers have described, under the title " David's disease ", non-thrombocytopenic purpura thought to be due to ovarian deficiency (Wintrobe 1951, Whitby and Britton 1953), but David's five cases ultimately became thrombocytopenic (David 1926), they were all women, but there is little to suggest that they had ovarian deficiency The following case is reported because it seems to be the first in which the relationship between the hæmorrhagic tendency and ovarian deficiency has been clearly shown

Case-report

A European woman, aged 38, was admitted in February, 1957 She had given birth to a live infant in 1947 by a normal delivery, and later had had three miscarriages In 1954 she began to have pain in her right iliac fossa for 2 or 3 days in each intermenstrual period In early 1956 she noticed a lump in the same region, later that year a benign cystic right ovary was removed, the left ovary and uterus appeared normal After this operation the intermenstrual pain ceased, but her next menstrual period resulted in profuse hæmorrhage for 7 days and a brown vaginal discharge for a further 10 days

She sailed from England in December, 1956, and during her second menstrual period after the operation a child on the ship fell on her, hitting her abdomen with its head She immediately had severe abdominal pain and vomiting When she arrived at Las Palmas she had a second laparotomy, and was found to have a small amount of blood in the abdominal cavity and a large band of adhesions matting down the small intestine to the uterus This band of adhesions had two bleeding-points which were ligated, and the intestine was freed from the uterus The left ovary was found to be atrophic

The second menstrual period continued for 3 weeks, and she had to be given a blood-transfusion During this period bruises began to develop on her limbs and abdomen She sailed from

Las Palmas at the beginning of January, 1957, but on the ship soon began to have nausea and severe abdominal pains in the suprapubic and left paraumbilical regions. The colic became very severe and bruises continued to develop.

She was admitted to hospital with severe abdominal colic immediately on arrival in Singapore. The only abnormal physical signs were the operation scars, large bruises on her legs and abdomen, and an internal congenital strabismus of her left eye with suppression of the left visual image. The abdomen was soft and not tender.

Investigation showed a weakly positive capillary-resistance test (Hess test with the cuff at 80 mm. Hg for 10 minutes), hæmoglobin 12.1 g. per 100 ml., white blood-cells 8300 per c.mm. (78% neutrophils, 19% lymphocytes, 2% monocytes, 1% eosinophils), thrombocytes 290,000 per c.mm. The thrombocytes appeared normal in stained dry films and in wet preparations. The bleeding-time, clotting-time, one-stage prothrombin-time, prothrombin-consumption time, clot retraction, plasma-fibrinogen, serum-proteins by electrophoresis, urinary diastase, and serum-amylase were all within normal limits. The urine contained no sugar or ketone bodies, and only a trace of albumin. The urinary deposit was microscopically normal, and the stool contained no occult blood.

Treatment and course.—It was thought that she had a hæmorrhagic diathesis producing bruising and abdominal colic (as in Henoch's purpura), and she was given 200 mg. of cortisone by mouth in divided doses on the 1st day, 150 mg. on the 2nd day, and then 100 mg. daily for a further 23 days. Injections of 40 units of long-acting corticotrophin were given twice weekly to minimise adrenal suppression.

There was no clinical response, the abdominal colic increased and frequent injections of pethidine became necessary to control the pain. Occult blood began to be present irregularly in the stools, and the capillary-resistance test became strongly positive. Repeated investigation showed no significant change in the hæmatological findings. A screening blood-coagulation test, in which the patient's plasma was mixed with varying proportions of normal plasma and was then recalcified at 37°C, showed that the platient's plasma clotted slightly more quickly than normal plasma. There was therefore no evidence of any blood-coagulation defect, and it seemed probable that the hæmorrhagic diathesis was due to increased capillary fragility alone.

The administration of calcium chloride 2 g. intravenously and ascorbic acid 500 mg. by mouth, and the transfusion of 450 ml. of fresh blood, produced no clinical improvement and no change in the strongly positive capillary-resistance test.

Since the hæmorrhagic tendency had become serious only after the removal of one ovary, and since the other ovary had been found to be atrophic, the patient was given a course of oral stilbœstrol in high dosage (40 mg. daily). Her condition gradually began to improve, and by the 3rd day of stilbœstrol therapy it was possible to stop the injections of pethidine. By the 6th day bruising had ceased and the capillary-resistance test was only weakly positive. Stilbœstrol was stopped after 17 days, and within 36 hours the patient again had bruises and severe abdominal colic. Pethidine had to be given again, and the capillary-resistance test became strongly positive. 7 days after the cessation of stilbœstrol therapy dienœstrol 6 mg. daily was started. Once again the bruising and abdominal pain gradually ceased, and the capillary-resistance test became negative on the 3rd day of dienœstrol therapy.

In hospital the patient was observed to have frequent transient losses of consciousness. These attacks ceased when she was given troxidone 900 mg. daily, but after 3 days an erythematous rash developed, apparently in relation to the drug, and administration was stopped. She was then maintained on phenobarbitone 180 mg. daily, and the attacks, which seemed to be petit mal possibly resulting from small hæmorrhages into the cerebral cortex, became much less frequent.

She was discharged at the end of March, 1957, and joined her family in North Borneo. She has continued on dienœstrol and phenobarbitone as above, and up to November, 1957, had only occasional bruises and minor attacks of colic. She still had occasional attacks of petit mal.

Discussion

Under the title "hereditary familial purpura simplex", Davis (1939, 1941) reported eighty-eight cases, eighty-four of them in women, in which there was evidence of a non-thrombocytopenic hæmorrhagic tendency. The bleeding-times, coagulation-times, and clot retraction were normal. Many had positive capillary-resistance tests, and in most cases hæmorrhagic symptoms began around the menopause. Davis found that the condition was common in women, and the present case may be another example of the same syndrome. This case is interesting because there is good evidence that the hæmorrhagic tendency became more evident after oophorectomy and responded to œstrogen therapy. It seems possible that patients with hereditary familial purpura simplex may also respond to this treatment.

In the absence of manifest allergic findings or a suggestive family history, it would be difficult to differentiate Schonlein-Henoch purpura of allergic origin from hereditary familial purpura simplex. Both Schonlein (1839) and Davis (1939, 1941) drew attention to the high incidence of rheumatic symptoms in their respective syndromes, and in both the only hæmatological and vascular abnormality seems to be increased capillary fragility. It seems probable that the two conditions differ only in their ætiology.

The congenital strabismus of the patient reported may be a purely coincidental finding, but the report of seven cases in a single family with increased capillary fragility, six of whom had ptosis (Fisher et al. 1954), raises the possibility of a similar hereditary connection in this case. One of their cases (in a woman, aged 32, with bilateral ptosis and a history of ecchymoses, four miscarriages, and hypermenorrhœa) closely resembles the case reported here.

Summary

A case is described of a woman in whom a hæmorrhagic diathesis developed, owing to increased capillary fragility following oophorectomy; this responded well to œstrogen therapy.

This syndrome resembles hereditary familial purpura simplex, which in turn resembles allergic Schonlein-Henoch purpura.

Hereditary familial purpura simplex may also be found to respond to œstrogen therapy.

This patient was admitted under the care of Prof. G. A. Ransome; I am grateful to him for permission to publish the case, and to Dr. H. Breitkreuz for interpreting the relevant German literature.

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Preliminary Communication

HYPERSENSITIVITY TO HISTONE
INDUCED EXPERIMENTALLY IN RABBITS *

An abnormal gamma-globulin has been found in the sera of patients with acute disseminated lupus erythematosus (L E), scleroderma, dermatomyositis, and certain forms of rheumatoid arthritis in which L E cells are present[1] This abnormal protein has been investigated histochemically by the fluorescent antibody technique[2] supplemented by enzymatic digestions and inhibition procedures, and has been shown to possess an apparently specific reactive affinity for intranuclear desoxyribonucleoproteins in autologous, homologous, and heterologous tissues A similar histochemical phenomenon in lupus patients has been described by Friou[3 4]

The constancy of the abnormal gamma-globulin in patients with the listed disorders and the resemblance between the intranuclear binding of nucleoprotein by gamma-globulin and the findings in immune reactions suggest that hypersensitivity to desoxyribose-nucleic-acid-proteins may play a significant role in the pathogenesis of some of the so-called diseases of collagen

To test this we have attempted to sensitise rabbits against heterologous nucleoprotein, in order to establish the immunological state supposed to exist in human patients, and perhaps even to create in animals an experimental disease state similar to, if not altogether identical with, that found in human systemic lupus erythematosis, scleroderma, and dermatomyositis

Methods

Albino rabbits were apportioned at random to groups (table I), each lot containing both males and females The antigen was commercial calf-thymus histone prepared by the method of Mirsky and Pollister,[5] dissolved in 0 2 M hydrochloric acid, and adjusted to neutrality with 1 0 M sodium hydroxide Rabbits in group I received, in addition to the nucleoprotein antigen, an adjuvant based on that of Fischel et al[6] (table II) Each dose contained the same constituents, but they were mixed in different proportions, and with the Fischel adjuvant a different antigen was used

Initial immunisation of the rabbits in group I was attempted by the intramuscular injection of two doses of the antigen-adjuvant combination described Each rabbit in group II was given intravenous histone 50 mg in aqueous solution, and those in group III were injected intramuscularly as their fellows in group I but received adjuvant alone A month later the rabbits were given subcutaneous booster doses of histone 50 mg

All the animals were bled periodically from the marginal ear vein, and their sera were assessed for antibody content by the indirect or "layering" fluorescent antibody technique Tissue substrates included autologous rabbit skin obtained by biopsy under local anæsthesia (procaine hydrochloride 1%), homologous rabbit liver and heterologous bovine aorta secured immediately after death, and heterologous human skin and placenta, obtained respectively at surgery and at delivery Fresh frozen sections were stained with rabbit serum and then counterstained with anti-rabbit gamma-globulin goat-serum conjugate Cross-inhibitions, as described elsewhere (Bardawil et al[7]), were performed between rabbit and human sera Stained sections were examined under a Reichert 'Zetopan' fluorescence microscope and photographed in colour upon 'Super Anscochrome' daylight emulsion with a 'Leica IIII' 35-mm camera with 'Micro Ibso' attachment

Results

Staining Reactions

Of the three animals in group I two died of concomitant infection the first week following injection The surviving rabbit, Adj H-1 (table I), first showed the presence of antibodies to histone 49 days after the initial injection of antigen and about

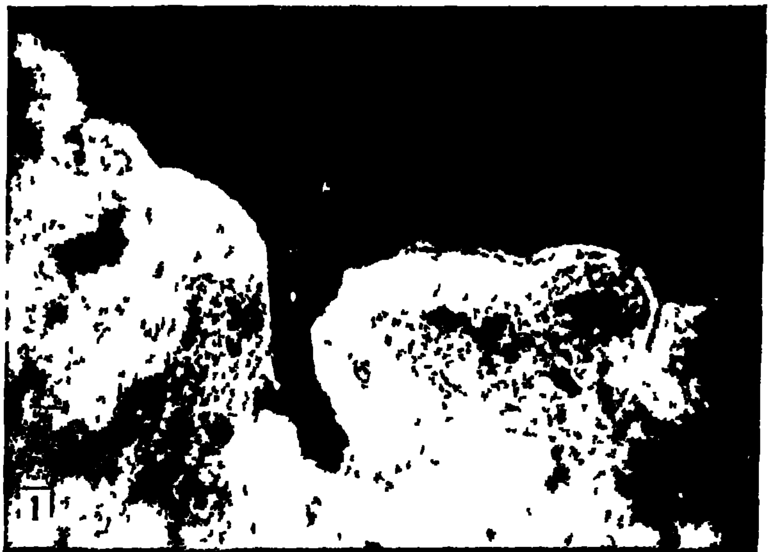

Fig 1—Autologous localisation of serum-gamma-globulin from rabbit Adj H-1 Note nuclear staining within superficial layers of epithelium

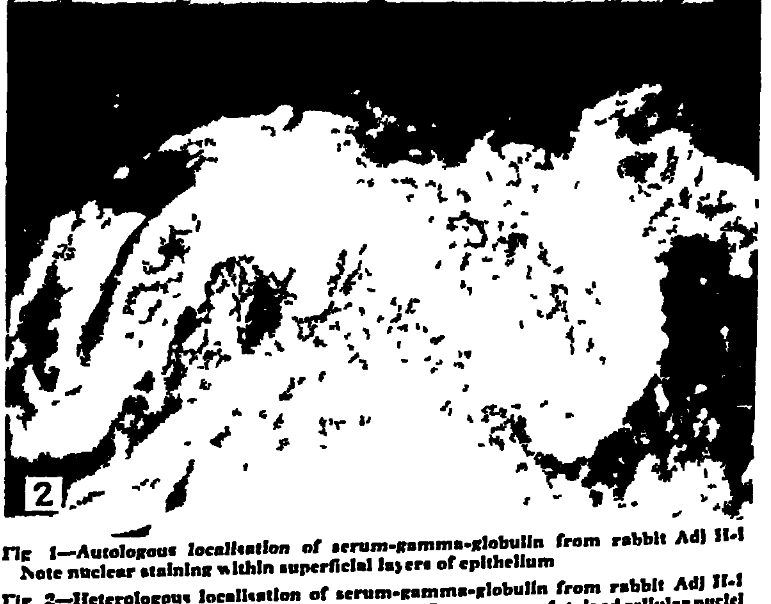

Fig 2—Heterologous localisation of serum-gamma-globulin from rabbit Adj H-1 Human skin as tissue substrate Note brilliant fluorescence of stained cellular nuclei

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* Supported by Grant C-2451 from the U S Public Health Service, Bethesda, Maryland, U S A

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2 Coons, A H *Int Rev Cytol* 1956 5, 1
3 Friou G J Finch, S C, Detre K D *Fed Pro* 1957, 16, 413
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5 Mirsky A F, Pollister, A W *J gen Physiol* 1946, 30 117
6 Fischel E E Kabat E A Stoerk, H C, Bezer, A E *J Immunol* 1952, 69, 611
7 Bardawil, W A, Toy, B L, Hertig, A T *Amer J Obstet Gynec* April, 1958, p 708

TABLE I—EXPERIMENTAL GROUPS

Group	Antigen	Rabbit	Result
I	Histone and adjuvant	Adj H-1	Nuclear staining
		Adj H-2	Died
		Adj H-3	Died
II	Histone	H-1	—
		H-2	—
		H-3	Died
III	Adjuvant	C-1	—
		C-2	—

15 days after the secondary dose The antibody level was estimated crudely by the intensity of nuclear staining, and was observed to increase gradually over about 55 days, thereafter declining until staining became weak, irregular, or (as it often did) disappeared A second booster injection, given to this rabbit about 10 weeks after the first, restored the capacity for intense intranuclear staining

Serum-antibodies in the hypersensitive rabbit are bound histochemically with intranuclear material in autologous, homologous, and heterologous tissues (figs 1 and 2) In addition to staining bovine nuclei, from which the antigen had been derived, the serum-gamma-globulin of rabbit Adj H-1 reacted also with rabbit and human nucleoprotein

In group II rabbit H-3 died during the first week after injection Rabbits H-1 and H-2 and the two controls in group III never produced antibodies measurable by the present technique The participation of the rabbits' own gamma-globulin was excluded by direct staining for this protein by techniques described elsewhere [7]

Because a direct conjugate of serum-globulin from rabbit Adj H-1 was not available, auto-inhibition was not attempted

TABLE II—SENSITISING SOLUTION

Dry antigen	50 mg	Aquaphor *	0 2 ml
Tubercle bacilli	0 5 mg	Mineral oil	0 4 ml

Modified from Fischel et al [6]

* Emulsifying agent made by Duke Laboratories Inc.

Serum from this rabbit has successfully cross-inhibited staining by a conjugate made from the gamma-globulin of a patient with active scleroderma

Collateral Tests

At the apparent peak of nuclear staining intensity in Adj H-1, 35 days after the booster injection, a positive Arthus reaction (local œdema and necrosis) was obtained by the intradermal injection of histone 1 5 mg An attempt to induce an Arthus reaction after the capacity for intranuclear staining had waned was fruitless, but an additional intradermal injection applied about a month after the second booster dose caused severe local hæmorrhage and necrosis Attempts to elicit similar responses from the rabbits in groups II and III failed

In attempted ring precipitations, rabbit and human sera were tested against neutral solutions of histone in multiple dilutions The results were inconclusive because both test and control sera precipitated the antigen at practically all concentration levels, perhaps because of the presence of calcium and magnesium cations in the sera

L E -cell preparations made with serum from rabbit Adj H-1 did not show typical inclusion bodies Blood-counts on the sensitised rabbit showed marked anæmia and leucopenia (lymphocytes 70%, segmented forms 29%, basophils 1%)

Discussion

In the surviving test rabbit (Adj H-1) hypersensitivity to histone, induced experimentally, led to the appearance of a circulating serum-antibody with a demonstrable reactive affinity for autologous, homologous, and heterologous intranuclear nucleoproteins The histochemical behaviour of this antibody seems to be morphologically identical with that of the so-called abnormal globulin or "L E factor" reported in human collagen disease The heterophil reactivity observed is to be expected in view of the demonstration by Allfrey et al [8] that desoxyribose nucleic acid from various sources—including calf thymus and kidney, chick erythrocytes, paracentrotus and trout sperm, and wheat germ—can restore to nuclei their capacity for synthesis after it has been destroyed by desoxyribonuclease Though nucleoproteins can mediate the most complex biological functions, they seem to remain sufficiently primitive to be immunologically non-species-specific

If one of the so-called collagen diseases is shown to have a definite basis in hypersensitivity against nucleoprotein, the experimentally noted lack of species specificity may be taken to imply that such allergy in the human patient may follow antigenic stimulation by viral, bacterial, or animal desoxyribonucleoprotein It has been found in this laboratory that positive sera stain ordinary smears of streptococci, including the viridans group Indeed, if a non-specific sensitisation against nucleoprotein is assumed, it is possible to construct a simple and orderly pathogenic theory to account for the classical morphological lesions found in the collagen diseases, embracing not only their character but also their topographical distribution in the body

Demonstration of the intranuclear binding of nucleoprotein is but the first step in the establishment of nucleoprotein sensitivity as a factor in the pathogenesis of some of the collagen diseases The cross-inhibition of serum from a patient with scleroderma provides additional suggestive evidence of a common process The most arduous task of all, that of inducing clearcut clinical disease in animals artificially, has not yet been accomplished

Summary

The histochemical behaviour of sera from human patients with certain so-called collagen diseases has been simulated by samples from an animal sensitised against bovine histone

Evidence is presented that the observed effect depends on immunological reaction, and the relation to human disease is discussed

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8 Allfrey, V , Mirsky, A E , Osawa, S The Nucleus and Protein Synthesis, in The Chemical Basis of Heredity (edited by W D McElroy and B Glass), pp 200 231, especially table 4, p 221 (listing of species) and p 218 ff Baltimore, 1957

"The fact that most students attend lectures has repercussions on their lecturers Having a good attendance, teachers may assume that their students must learn a good deal from them, or else they would not attend Accordingly, any lecturer who does not come into close contact with students in laboratory classes, or in other ways, can very well live in a pleasant dream-world about the effectiveness of his teaching Perhaps the easiest and cheapest way to improve university teaching about one hundred per cent would be to make it compulsory for every lecturer to spend a good deal of time with his students immediately after each lecture to find out what they did, and did not, learn from it "—ARTHUR W HAM, *Canad med Ass J* 1958, 78, 482

Reviews of Books

Principles of Gynæcology

T N A Jeffcoate, M D, F R C S E, F R C O G, professor of obstetrics and gynæcology, University of Liverpool London Butterworth 1957 Pp 696 75s

Professor Jeffcoate's new book will be welcomed by the reader who wants more than a standard textbook of factual knowledge In his preface he says that the book is aimed at the undergraduate at the top of the class, but because the emphasis throughout is on the assessment and treatment of the patient as an individual rather than as a case, it could equally well be said that the book is intended for the student who wishes to become a good doctor Description of operative technique is omitted, but symptoms and diagnosis are very fully discussed There are excellent chapters on problems of sex and marriage, hormone therapy, genital cancer, and many other subjects of daily importance to the family doctor The book is essentially practical Short illustrative case-histories and hints from the author's wide experience increase its value

The headings and layout are clear, the illustrations, including twelve colour plates, excellent, and the index comprehensive As a matter of policy no references are given, it is perhaps a pity that a book that so stimulates the interest does not give any guide to further reading and does not provide students "at the top of the class" with brief biographical footnotes about the famous names in gynæcology A few subjects, such as intersexuality, developmental anomalies, and bladder function are described in detail perhaps unnecessarily great for the non-specialist reader They are subjects, however, which have important practical applications and on which much light has been shed by Professor Jeffcoate's own researches and writings

The book can be confidently recommended not only as a textbook on medical gynæcology but also as an excellent thesis on the proper balance between the scientific and the humanistic approach to a subject in which psychosomatic factors are important

Respiratory Disease and the General Practitioner

C M C Toussaint, M R C S, D P H, consultant chest physician, Willesden Chest Clinic and Central Middlesex Hospital, London, president, British Tuberculous Association, 1957–58 London National Association for the Prevention of Tuberculosis and Diseases of the Chest and Heart 1958 Pp 28 7s 6d

This useful handbook deals with the three major respiratory diseases—pulmonary tuberculosis, lung cancer, and chronic bronchitis The sections on pulmonary tuberculosis and lung cancer are excellent essential features have been selected with an unerring eye, and are set out with admirable clarity and conciseness Important points are emphasised by illustrative case-reports and radiographs The only shortcoming is the rather dogmatic approach to the management of pulmonary tuberculosis it seems injudicious, for example, to advocate one year's chemotherapy in preference to a longer period when the general practitioner's adviser on the spot may, possibly rightly, have other views The three pages on chronic bronchitis fall below the generally high standard, but this is nevertheless a splendid little book As a guide to the early diagnosis of pulmonary tuberculosis and lung cancer it could scarcely be bettered, and we warmly recommend it to the general practitioner

Body Water in Man

Maurice B Strauss, M D, professor of clinical medicine, Boston University School of Medicine London J & A Churchill 1958 Pp 286 50s

The title of this book seems to invite comparison with the monograph on Body Water by the late J P Peters, to whom it is dedicated In many ways the book is worthy of this comparison, for it is readable, scholarly, and critical, and manages to illumine a thorough survey of the literature with interesting allusions to comparative physiology There are more non-American references than is usual some of those, as to Homer, Sallust, and the Bible, are no doubt obligatory and pre-Columbian, but others are facultative

The treatment of the subject is centred on physiology, but clinical information is introduced where it illustrates physiological principles This allows a more leisurely treatment of the intake and output of water and salt than is commonly found in similar works The core of the book is an outstanding account of antidiuretic hormone, and the factors which stimulate or prevent its production, adrenal hormones are more cursorily dealt with, and this is perhaps surprising in a book which emphasises volume rather than osmolarity The studies of Wirz on the renal action of antidiuretic hormone are not mentioned, and there is only casual reference to potassium, on which the volume of intracellular fluid largely depends

Although the book does not perhaps fulfil all the title promises, it can be recommended as a critical review of the mechanisms regulating the amount of water and salt in the body

Drugs, Their Nature, Action and Use

Harry Beckman, M D, director, department of pharmacology, Marquette University Schools of Medicine and Dentistry Philadelphia and London W B Saunders 1958 Pp 727 105s

Professor Beckman's new textbook of pharmacology is designed chiefly for undergraduate students The brief opening section, the pharmacologist's apologia, is followed by eight general chapters on drugs and their actions The third section, the major part of the book, deals with individual drugs in much detail, and each chapter or subchapter is rounded off by a useful list of references Those who are familiar with Professor Beckman's writing will look forward to a lively and entertaining book as well as a sound text of pharmacology—and they will not be disappointed Some readers will disagree over details and points of emphasis, but in the main there is very little with which they can quarrel

It is hard to say who will find the book most useful Most medical students in this country would probably consider it both too expensive and too detailed for use as a standard text, but they will find it very helpful when they need a fuller yet concise account of a particular drug, and for this reason it should be in every medical school library Although it is less comprehensive than some other large American textbooks of pharmacology, it could be used with advantage by physicians as well as pharmacologists, they will both appreciate it for its sound common-sense pharmacology and its pleasant and easy style

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A Woman Doctor Looks at Love and Life (London Macmillan 1957 Pp 190 8s 6d)—Dr Marion Hilliard is the lately retired chief of obstetrics and gynæcology at Women's College Hospital, Toronto, and her book is one of advice to women from adolescence to old age, with a word to husbands, based on her experience of hospital and private practice and of her own (single) life She writes in colloquial Canadian which strikes oddly on the English ear, and the implied social and medical background of urban Canada is strangely different from our own, but there is much wisdom, tinged with humour, in her chapters (that on the menopause is a happy example), and she has an acceptable philosophy—though most things in life are inevitable they can be turned to good account

Connective Tissue (Oxford Blackwell Scientific Publications 1957 Pp 363 42s)—In 1956 the Council for International Organisations of Medical Sciences held a conference in London to expound and coordinate modern views on connective tissue Speakers came from East and West Europe, the United States, and South Africa Nomenclature and chemical methods were much discussed The proceedings have been edited (under the direction of Prof R E Tunbridge, the chairman) by Dr Madeline Keech, Dr J F Delafresnaye, and Dr G C Wood

THE LANCET

LONDON 26 APRIL 1958

The Snows of Yesteryear

To most of us the passions and protestations, the charges and countercharges, the hostilities and heroism of the winter of 1956–57 are mere scraps of memory they have become the raw material of the historian and social scientist It is seventeen months since the first plane-load of Hungarian refugees were welcomed in this country on a wave of popular sympathy Within a few months their number was to increase to 20,000, and they were soon followed by more than 7000 evacuees from Egypt This first phase of the refugee saga was one of crisis and achievement The crisis arose from the need to provide, almost at a moment's notice, thousands of destitute people with shelter, food, and all the basic necessities of life The achievement was the work of voluntary organisations which successfully completed this task These philanthropic bodies, always the butt of the cynical and the sophisticated, have had to face many difficulties in recent years, with the inauguration of the Welfare State even some of their friends questioned their continued value No such doubts remained in the minds of those who observed their work in the last days of November and the early days of December, 1956 That "the rapid success of the Hungarian refugee operation, and the slower but no less praiseworthy achievements in the more difficult task of resettling the Anglo-Egyptians, may be ascribed, above all, to [their] effort" is one of the conclusions in *Refugees in Britain*, a P E P pamphlet[1]

These organisations depended on the generosity of countless individuals, and they benefited from the Government's moral support, but individual charity had to be harnessed, and there was an inevitable time-lag before official organisations began to function During the vital first weeks, while the British Council for Aid to Refugees (the Government organisation set up to cope with the emergency) tumbled from crisis to crisis, the British Red Cross Society and other voluntary organisations were able to call on the immediate services of a highly trained, well-disciplined, and devoted body of workers, and, unhampered by the need to formulate long-term policy, they grappled with the difficulties at hand These included the provision of medical cover at reception stations and in transit camps, the accommodation of the sick in hospital (where interpreters were required even for rudimentary history-taking), and the maintenance of communication between hospital patients and their families While local practitioners and medical officers on loan from the Armed Forces gave first-aid and casualty service, the sudden influx of several thousand apparently fit immigrants raised a formidable public-health problem It is difficult not to sympathise with critics who later deplored that medical cover did not include, from the start, preventive measures, especially radiographic screening for tuberculosis[2], but this was not an act of official ineptitude, nor was it due to lack of foresight by individual medical officers of health It is possible to argue that present-day immigration policy, which takes no account of disease dissemination, is inspired by the ostrich rather than by the spirit of SNOW, but there is no doubt that the official attitude towards the Hungarian and Anglo-Egyptian refugees was in full accord with this policy

The weeks of emergency and improvisation were followed, inevitably perhaps, by a period of disenchantment on the part of the refugees and of frustration on the part of their hosts A striking observation in *Refugees in Britain* is the similarity between the mental reactions of two such widely different groups of people as the Hungarians and the Anglo-Egyptians

> "It might have been expected that the Hungarians would be particularly amenable, being filled with gratitude for the help and generosity of the British people, while the Anglo-Egyptians would be embittered at being expelled from Egypt and insistent on the duty and responsibility of the British Government towards them There were Hungarians who were extremely grateful, and Anglo-Egyptians who were disgruntled, but the distinction is by no means so clear cut"

It took doctors and administrators several months to realise that refugee existence itself imposes on its victims a distinct pattern of behaviour, and the psychological basis of this behaviour is still far from clear Certainly many factors are involved they range from temporary casting-away of certain social inhibitions (an action familiar to every holiday tripper) to complex feelings of guilt towards those left behind *Refugees in Britain* mentions but a few of its manifestations, such as the insistence of many highly educated refugees that behind the ill-advised but well-meant assurance given to them in Austria—that Britain would only be a transit station to America—lay a diabolical ruse to acquire cheap labour This state of mind was often reflected in psychosomatic illness, and it is fortunate that both mental and physical disturbances only rarely left permanent scars

The third phase in the life of the refugees was a gradual return to normality, and this significantly coincided with the recognition by the authorities that the key to resettlement was permanent employment In this respect, says the P E P pamphlet, "the Hungarians were one of the most promising bodies of refugees to arrive in this country" An early check (later confirmed by random samplings) showed that 70% were aged between eighteen and thirty-five, they had not been demoralised by long periods in refugee camps Of nearly 15,000 who had remained in the United Kingdom, only 617 were still registered as unemployed at the end of December, 1957, and only about 1500 (who included dependants, unaccompanied children, and students) had not yet been settled in permanent employment Despite the absence of a language barrier, the permanent resettlement of the Anglo-Egyptians proved a far more difficult task "They were mainly in family groups, many middle-aged or elderly, and usually with a background of commercial and administrative work" Some have refused work because the standard was below what they had been accustomed to some are still delaying in the hope that they may eventually be allowed to return by the Egyptian Government Of the Anglo-Egyptians who had been originally accommodated in hostels 50% were still there at the end of 1957, compared with only 10% of the Hungarians

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[1] Refugees in Britain Hungarians and Anglo-Egyptians *Planning* 1958, 24 no 419 Published by P E P, 16, Queen Anne's Gate, London S W 1 Pp 35 2s 6d

[2] See *Lancet*, March 29, 1958, p 686

There remains a "hard core" of unsettled refugees from both groups, and, in the case of the Hungarians, this includes a small proportion of adolescent delinquents But in more than this narrow sense the refugee problem, like yesteryear's snow which haunted the poet, is still with us Throughout the world refugees are thought to number little short of 2 million—an estimated 250,000 in Europe, 915,000 Palestine Arabs, 700,000 mainland Chinese in Hong Kong, and 10,000–15,000 Europeans (mostly White Russians) in China and Hong Kong[3] Of these Mr CHRISTOPHER CHATAWAY and his colleagues[4] write

> "We talk of tolerance, justice, and the dignity of mankind, and all over the world we find stagnant pools of humanity, who have been robbed of all these things, who stand behind wire, dragging their uncovered roots, friendless, soilless, waiting for ground in which they may grow again into citizens Their presence mocks loud at our pretentions of civilisation How enlightened can we be when so many plain people are cast out by fear?"

CHATAWAY and his colleagues believe that a World Refugee Year, in which Britain should play a leading part, would go far towards solving this vast problem

Chimeras and Antibodies

INSIGHT into the mechanism of antibody formation can be gained by studying the effects of irradiation Animals subjected to whole-body irradiation with X rays die from hæmorrhage, anæmia, and infections Sometimes the blood-forming tissues are completely destroyed, and erythrocytes, leucocytes, and platelets disappear from the blood (but this can be prevented by shielding the spleen from radiation) When the blood-forming tissues are destroyed the irradiated animal may still survive if a suspension of bone-marrow from a normal animal is injected intravenously The blood-forming tissues apparently return to normal a few days after the injection, and the regenerated bone-marrow and peripheral blood-cells in the treated animal are derived from the donor cells Usually, of course, grafts from other animals do not take, but in these irradiated animals *not only* are the blood-forming tissues destroyed but the immunological mechanisms are damaged, and the irradiated animals accept grafts which would be rejected by normal animals The regenerated tissues being derived from the donor tissues, the way is open to colonisation by further grafts, compatible with the donor, that would be rejected by the recipient animal if it had not been irradiated

The obliteration of the heterologous-graft-destroying mechanism by irradiation raises the possibility of producing chimeras Thus mice receiving a lethal dose of X rays can be saved by the injection of bone-marrow cells from a normal rat, and, in the treated mice, rat granulocytes are found in the blood-forming tissues and rat platelets in the blood But, although these chimeras survive the radiation damage for a month, they may subsequently lose weight, and they have a high mortality-rate Immunological intolerance of the foreign cells develops gradually, in some cases the host animal rejects the donor cells, and at times the foreign donor cells show an immunity response to the tissues of the host The transplanted cells can transfer specific sensitivity to certain tumours from the donor to the irradiated recipient animal The more dissimilar the donor and recipient, the larger the dose of myeloid cells required to save the irradiated animal and the shorter the survival-time, whereas isologous grafts among members of the same closely inbred strain of animals are the most effective

The contribution of the study of irradiated animals to the elucidation of immunological problems is evident from the account of a symposium[1] sponsored by the Oak Ridge Laboratory in Tennessee The symposium dealt primarily with bone-marrow transplantation in irradiated animals, but its scope included recent work on antibodies Although the immunological work is not always directly connected with the main subject of the symposium, it is clearly related and forms a link with results derived from different methods of study It is reported, for example, that turkey erythrocytes appear *in the circulation of chimeras* produced by grafting adult turkey spleen on to the chorioallantois or into the cœlom of chick embryos—an observation immediately reminiscent of work on radiation chimeras The identity of the cells responsible for antibody formation has long been debated, and it was suggested at the symposium that a large pyroninophilic cell, derived from a primitive fixed reticular cell, may be responsible After antibody has been formed as a result of the primary antigenic stimulus, these large cells are transformed into either small lymphocytes or mature plasma cells, which then disappear from the spleen and probably enter the circulation These suggestions may be considered in the light of a hypothesis put forward by SPEIRS,[2] who postulates a two-stage effect The first effect of introducing antigen into the body is migration of granulocytic cells into the area, and there is a specific eosinophil response if the host has been previously exposed to the antigen The antigen induces specific enzyme formation in the eosinophil cells, which are then subjected to phagocytosis by reticulo-endothelial cells These in turn utilise the specific enzymes from the ingested eosinophils to form antibodies While antibody is being formed the reticulo-endothelial cells undergo nuclear changes, becoming increasingly pyroninophilic and being transformed into plasma cells

It is becoming clear that, although antibodies appear to be normal serum-globulins modified so that they react specifically with the appropriate antigen, they *are not* formed by modification of pre-existing globulins *but are* synthesised de novo from the aminoacid pool in the body The complete synthesis of an antibody molecule from the constituent aminoacids takes less than half an hour—an achievement which dwarfs the mightiest efforts of the organic chemist. The chemical mechanism by which antibodies, or indeed any proteins, are synthesised is obscure, but it seems that specific nucleic acids from the cell nucleus play a part in organising the arrangement in proper sequence of aminoacids in the polypeptide chains of the protein molecule. Hypotheses as to how nucleic acids effect this organisation tend to become more complex, and a current suggestion is that the specific antigen modifies deoxyribonucleic acid in the cell nucleus, conferring a heritable change. This modified nuclear deoxyribonucleic acid, it is suggested, transfers appropriate specificity to ribonucleoprotein templates responsible for organising the synthesis of antibodies. These templates, in conjunction with high-energy phosphate bonds in adenosinetriphosphate, are regarded as activating aminoacids so that appropriate ones are brought into juxtaposition and react together to form the specific polypeptide chain of aminoacids. Once antibody formation has been initiated, the amount of antibody present in the body at any time is the resultant of a dynamic equilibrium between the synthesis of new antibody molecules and the degradation of old ones back to aminoacids. Antibodies to the same antigen are not identical and their breakdown-times vary. In the case of Forssman antibodies to sheep red blood-cells in a rabbit, for example, the half-life of the antibodies present varied from 2·8 to 5·6 days.

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[3] *Crossbow*, Spring 1958, p 10

[4] Chataway, C, Jones C., Philpott, T *ibid*

[1] *J cell comp Physiol* 1957, 50, suppl 1

[2] Speirs, R S *Nature Lond* 1958, 181, 681

Turning to the interaction of antigens and antibodies, in the case of protein antigens it is the carboxylic-acid groups of the antigen that react with amino groups of the antibody molecule. Some indication of the size of the combining sites of antigen and antibody has been obtained in the case of antibodies to dextran. Inhibition studies show that the combining sites are larger than three glucose molecules and approximate to the size of a hexasaccharide. All evidence, however, indicates that antibodies are heterogeneous, and the antibody to any specific antigen cannot be regarded as a precisely constituted chemical compound of reproducible properties. In fact the antibodies present in a single animal at any one time differ widely. As more is learnt about immunology the subject becomes more complex rather than simpler.

Annotations

LEADERS IN RESEARCH

LEADERSHIP in research is a subject of great moment not only to scientists but also to the general community. Few people are better fitted to discuss this subject than Sir Charles Harington. In the first Russell lecture at St. Andrews[1] he had some telling things to say about the career of pure research—pointing out that, although its appeal to the young may be overpowering, there is a risk that in middle age it may prove emotionally unsatisfying, and that a little contamination with teaching or administration may be more satisfactory in the end for many people.

Sir Charles deals with leadership under the headings of Universities, Industry, and Government-supported research. He finds that in the long run leadership is a matter of unselfishness and kindness, in this the *Führerprinzip* has no place. The good leader helps to encourage collaboration between unrelated departments, to see possible fundamental discoveries in routine work, and to guide interest into paths likely to be profitable, and he is always on the alert to spot talent and encourage originality. Thus he aims to foster in the universities new ideas and lively teaching, in industry any work, bearing on the business, which has possibilities of originality, and in Government-supported institutions freedom combined with use of the vast resources which only the State can provide to foster work of value to the public. Sir Charles is as hesitant to direct the leaders as he suggests they should be in directing their own staffs, but he gives them, largely by implication, detailed advice which illuminates the way in which he has learnt to exert the best kind of leadership himself.

He says, quite rightly, that he is talking about leadership, and therefore gives little space to the kind of research that is not susceptible of direction. But it may be thought that he dismisses too easily the kind of research which consists, in his own words, in "seeing correlation between items of knowledge at first apparently quite unrelated". At its best such work (of which one example is Hunter's sudden perception of the relevance of the flushing of the deer's antler, after tying the artery, to the possible treatment of a popliteal aneurysm) requires a mental activity that was described by Livingston Lowes in *The Road to Xanadu* as the essence of genius. Sir Charles Harington maintains that this kind of discovery was characteristic of the early history of Science, and he adduces the sudden leaps forward in the arts, followed by "periods of stunned assimilation", as a parallel. He contrasts this with the continuous growth of Science today, with fact being piled on fact, each advance depending heavily on what has gone before. This analysis ignores the fact that the innovators in the arts were seldom the people who exploited the ideas: fugues were not invented by Bach, symphonies by Beethoven, or leitmotivs by Wagner. The impact of genius on research is as significant today as it ever was: if thought of in terms of discoveries per half-century, it is even more so. What else was Fleming's original observation which led to the discovery of penicillin? Sir Charles rightly stresses that a leader may help his staff to draw the significant conclusion from routine observations and may do much to encourage the power of observation. It is surely useful for the man who can jump to far-reaching conclusions to have a team working with him, who not only exploit the original idea but learn at first hand the significance of the notion that such ideas are possible.

RETROLENTAL FIBROPLASIA

Crome[1] has lately described, under the title "retrolental fibroplasia", 2 cases of bilateral detachment of the retina in infancy. In the first of these, a premature baby had received supplemental oxygen after birth, and besides retinopathy had a patent ductus arteriosus, renal calcinosis, and some evidence of encephalopathy. In the second, a full-term infant who was not subjected at any time to hyperoxia had detachment of the retina together with widespread congenital abnormalities In discussing these and other similar cases, Crome supports the view that retrolental fibroplasia is not always a local intraocular condition, but is only one manifestation of a disease that may involve other tissues, especially the central nervous system

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[1] Leadership in Scientific Research. Sir David Russell memorial lecture no. 1. By Sir CHARLES HARINGTON. London: Oxford University Press. 1958. Pp. 27. 3s. 6d.

[1] Crome, L. *J. Path. Bact.* 1958, 75, 163.

When Terry[2] introduced the term "retrolental fibroplasia" in *1942*, he intended to differentiate the lesions he was describing from the heterogeneous group of conditions long known under the nebulous but useful title of "pseudoglioma"—a group including all those conditions wherein the white pupillary reflex of retinal glioma was simulated, ranging from developmental abnormalities (such as persistent hyperplastic vitreous) to acquired changes (such as metastatic uveitis) Terry suggested three criteria for the condition he named prematurity, bilateral lesions, and their first appearance after birth Associated somatic or neurological abnormalities were not included It is now common knowledge that the disease for which these criteria were stipulated results from the administration of supplemental oxygen to the premature infant The causal relation of ambient hyperoxia to intraocular changes is very striking and has been abundantly proved, both by the production of analogous changes in laboratory animals[3-5] and by the virtual disappearance of the condition when administration of oxygen is controlled[6, 7] Thus exposure to hyperoxia may now be added to the three original criteria

In 1946, however, Krause[8] reported 18 cases which were similar to those of Terry, but in many of which there was also mental retardation, hydrocephalus, or other cerebral lesions, and Krause therefore proposed the term "encephalo-ophthalmic dysplasia" Rereading his paper with the knowledge we possess today, we find that Krause was applying the name to cases of different types, in 5 the eye changes were clearly congenital *Examples of so-called retrolental fibroplasia have been* described in which either oxygen was not given[9-11] or the infants were full-term[12, 13] But close examination of these reports shows that the name is being applied descriptively to conditions ætiologically dissimilar—the later stages of oxygen-induced retinopathy are in no way specific and may result from a wide variety of causes Similar intraocular damage has been observed not only in the other pseudogliomas but also in hereditary diseases such as incontinentia pigmentosa,[14] and it has been induced experimentally both by anoxia[15] and by vitamin deficiency[16]

Ending this confusion will depend largely on whether oxygen-induced retinopathy of prematurity may be accepted as a distinct entity not essentially associated with extraocular abnormalities Unfortunately it is impossible to be certain that the effects of oxygen exposure are confined to the eye, because there is a lack of data on the incidence of general somatic abnormalities in cases with and without retinopathy, *there is no agreement* on the significance of associated mental retardation,[17, 18] and, the disease not being lethal, necropsy reports are few Nevertheless, it seems that there is no obvious pattern of general somatic or neurological abnormalities consistently associated with oxygen-induced *retinopathy*, most cases are entirely free from extraocular abnormalities, and there is good evidence that *in laboratory* animals the damaging effects of long-continued hyperoxia are confined to the retina[19, 20] Hence there are no sure grounds for believing that any neural or somatic abnormalities are ætiologically related to concomitant oxygen-induced retinopathy

What then are we to call the type of case reported by Crome? It would probably be better now to abandon the name retrolental fibroplasia (which in any case is not particularly appropriate) and to replace it by "oxygen-induced retinopathy of prematurity", an extension of the name first proposed by Heath,[21] and to reserve this strictly for cases where the retinopathy develops after birth in premature babies subjected to hyperoxia The old term "pseudoglioma" may be retained for cases where the cause is uncertain or unknown Thus Crome's first case would be termed "oxygen-induced retinopathy of prematurity with associated abnormalities" and his second case "pseudoglioma with associated abnormalities"

PROGNOSIS IN RHEUMATOID ARTHRITIS

In trying to decide whether to use or to withhold a potentially dangerous drug in a case of rheumatoid arthritis the clinician must consider not only the risk and the possible benefits of treatment but also the seriousness of the disease in his patient Accurate information about *the benefits of treatment* can be gleaned only by the laborious method of controlled clinical trial Information about prognosis is no less difficult to obtain, involving as it does protracted study of a large enough group of patients to contain examples of the many types of course which the disease may follow Such studies have yielded fairly consistent figures for the amount of disability to be expected in each such group after various periods of time They have also made it possible to predict, though not as yet very accurately, the probable course in any individual patient

The rheumatic unit in Edinburgh has kept under close observation a group of patients with rheumatoid arthritis admitted to hospital between 1948 and 1951 Most of these patients have been watched for six years, and the changes in their condition have been described by Duthie and his colleagues[22] On admission to hospital 22% of the patients were unable to work or to look after themselves without help Incapacity of this degree must have arisen mainly from active inflammation in the joints rather than from advanced irreversible deformity and damage, for at the time of discharge from hospital only 0 4% remained in this lowest category of functional capacity This group of severely disabled patients is bound to be enlarged, as the years pass, by the added restrictions of old age and by fresh onslaughts of active-disease, that it should still account for no more than 9% of the whole series six years after discharge is gratifying Although the criteria used in similar investigations elsewhere have varied, this figure is close to the 10% found by Ragan[23] as the proportion of patients confined to bed or chair after five years of observation At the opposite end of the scale are the patients—11 3% of the total—who were fit for all normal activities when they left hospital After two years, in which some patients with moderate disability improved, the figure had risen to 28% During the next four years this group diminished only slightly This is again in keeping with experience in the U S A —in New York Ragan found no remaining evidence of arthritis in 26% of his cases (with another 22% suffering no more than occasional joint pains), and in a carefully analysed series from the Massachusetts General Hospital Short et al[24] found 13% of their patients in remission after an average of fourteen years of observation

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[2] Terry, T L *Trans Amer Ophthal Soc* 1942, 40, 263
[3] Ashton, N Ward, B, Serpell, G *Brit J Ophthal* 1953, 37, 513
[4] Patz, A, Eastham A, Higginbotham, D H, Kleh, T *Amer J Ophthal* 1953, 36, 1511
[5] Gyllensten, L J, Hellstrom, B E *Acta pædiat, Stockh* 1954, 43, suppl 100 p 131
[6] Yankauer, A, Jacobziner, H, Schneider, D M *N Y St J Med* 1956 56, 1474
[7] Parmelee, A H, Jr, Pilger I S, Austin, W O *Calif Med* 1956, 84, 424
[8] Krause A C *Arch Ophthal, Chicago* 1946 36 387
[9] Coxon, M W *Trans Ophthal Soc U K* 1951, 71 591
[10] Minton J, Cole P *Brit med J* 1951 i, 450
[11] Gordon, H H, Lubchenko L, Hix, I *Bull Johns Hopk Hosp*, 1954, 94 34
[12] Reese A B Stepanik J *Amer J Ophthal* 1954, 38, 308
[13] Reese, A B Payne, F *ibid* 1946 29, 1
[14] Scott J Friedmann A J, Chitters, M, Pepler, W J *Brit J Ophthal* 1955 39 276
[15] Ingalls T H Tedeschi C G Helpern, M M *Amer J Ophthal* 1952 35 311
[16] Warkany, J, Schraffenberger, E *Arch Ophthal, Chicago*, 1946, 35, 150
[17] King, M J *ibid* 1950 43, 694
[18] Potter, C T *Proc R Soc Med* 1954 47 715
[19] Ashton N *Amer J Ophthal* 1955, 39 153
[20] Patz, A *ibid* 1954, 38 291
[21] Heath, P *Arch Ophthal, Chicago*, 1950 44 245
[22] Duthie, J J R Brown, P E, Knox, J D E, Thompson, M *Ann rheum Dis* 1957, 16, 411

In the Edinburgh study treatment consisted in a "basic regimen" in hospital of rest in bed, the application of plaster splints to affected joints, the largest tolerable doses of aspirin, physiotherapy, and a graduated return to the highest attainable functional level The Boston patients were kept in hospital for a shorter time than those in Edinburgh, otherwise the programmes of treatment did not materially differ The two groups of investigators agree that patients admitted to hospital early in the course of their disease fare better than those admitted later, in Boston 37% of those admitted in the first year of their disease were in remission after observation extending in the majority to at least five years from discharge, only 4 7% of patients admitted later in the course of their disease did as well as this In Edinburgh 43% of patients admitted in the first year but only 10% of those admitted between the fifth and tenth year were free from any restriction in activity six years after discharge

The time of admission to hospital largely reflects the pattern of the disease thus cases admitted soon after onset will in general be those in which the disease has progressed rapidly, and in which disability arises mainly from inflammation in the joints rather than from irreversible anatomical damage In cases admitted later the disease clearly has either failed to abate after several years of continuous or intermittent activity, or has produced permanent damage It is not surprising that these two broad groups should differ in prognosis The Edinburgh report draws attention to two groups not included in its material—milder cases in which treatment in hospital is not thought necessary, and cases in which the patient never seeks medical help The second of these categories has been estimated[25] to account for 38% of women and 19% of men with rheumatoid arthritis

As regards other considerations helpful in prognosis the Edinburgh and Boston groups agree that men do rather better than women, and that an acute onset and a rapidly progressive course in the early months is favourable, a good response to treatment in hospital also augurs well for the future Finally it is becoming clear that the presence or absence in serum from cases of rheumatoid arthritis of the factor which agglutinates sensitised sheep erythrocytes has an important bearing on prognosis, in that patients with a negative agglutination test do well Duthie and his colleagues found a direct relationship between functional capacity and the concentration of the agglutinating factor

Although patients admitted to hospital early in their disease are a selected group, and probably likely to fare better than average however treated, few clinicians would seriously doubt the value of a period of treatment in hospital Like most of the other elements in the "basic regimen", treatment in hospital has not been, and should not be, submitted to controlled trial The patients whose course has been so closely studied in Edinburgh were treated by these sound and uncontroversial methods in a unit largely concerned with the problem of rheumatoid arthritis While there are no comparable figures for patients who have had less comprehensive care, there can be little doubt that the programme of continuous treatment and supervision, supplemented by skilled assistance in the solution of domestic and employment difficulties, contributed to the maintenance of independence and the ability to earn a living in so high a proportion of patients It is against results of this sort that any alternative or supplementary method of treatment must be measured

OLD PEOPLE AND THEIR FAMILIES

AN important investigation into the relations between old people and their families is described by Mr Peter Townsend,[1] who has based his observations on old people selected at random in Bethnal Green He visited over two hundred families, and it speaks volumes for his tact and patience that his searching questions were readily answered Several notable facts stand out Comparatively few old people were seriously isolated Many who lived alone had relatives nearby but preferred to maintain a "supported independence", seeing their families every day but not sharing a roof with them Their family interests embraced three generations, and each old person had on an average thirteen members of such an extended family living within a mile and kept in touch with most of them The elderly women were by no means passengers, and although they had much help from female relatives they made their own contribution when they could by providing midday meals, by caring for grandchildren, and in other ways This contribution by the grandmother gives her a permanent and valued role in the family and contrasts with the tragic uselessness that retirement brings to many men, when their income falls and they are excluded from their former social activities and cut off from their friends

About one in five of the old people had no children to support them Not all of these "isolates" complained of feeling lonely, a sense of loneliness affected principally those who had recently been bereaved or separated from their families, a group which Townsend calls "the desolates" But those without children were making the biggest demand on the social services At a local geriatric hospital the proportion of childless and unmarried among the patients was 43%, compared with 18% among the elderly population of Bethnal Green as a whole, and figures were similar among the occupants of a local welfare hostel and those in receipt of home help Townsend produces convincing figures to show that, as the variations of family circumstances are followed through to those with sons and daughters-in-law but no daughters, to the childless, and finally to the unmarried, the availability of family help diminishes and the claims on the social services increase This is particularly noticeable in single or widowed men who once they become infirm are much less independent than old women Various estimates suggest that but for the help given by female relatives the number of old people seeking admission to geriatric hospitals and welfare homes might be three to five times greater than it now is

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[23] Ragan, C *J Amer med Ass* 1949, 141, 124

[24] Short, C L., Bauer, W , Reynolds, W E Rheumatoid Arthritis London, 1957

[25] Kellgren J H., Lawrence, J S Aitken-Swan J *Ann rheum Dis* 1953, 12, 5

[1] Townsend, P The Family Life of Old People. London Routledge & Kegan Paul 1957 Pp 284 30s

About two-fifths of Townsend's subjects were infirm or living with an infirm spouse, and one in three had been in hospital within the past five years (A similar proportion of "infirmity", defined as confinement to a house or restriction of outdoor activity, was found in Sheffield [2] and in a London suburb [3]) One in eight had caused a relative to give up paid work in order to look after them, and at least to this extent were imposing a strain upon their families

What can be done to support the family in its task? Townsend suggests a comprehensive family help service, to experiment with alternatives to institutional care—boarding out the isolated, transforming old houses into self-contained one-room flats with housekeepers in charge, and finding accommodation for relatives This service would also extend the existing home-help arrangements to relieve overburdened relatives in the evenings and for holidays Already the home-help service is of the greatest value and could profitably be expanded [4], and, as Chalke [5] has observed, its worth cannot be measured merely in terms of hours of work In a few places night attendants enable the relatives of old people who are restless at night to get an occasional unbroken night's sleep Sometimes an infirm person cannot stay at home because a daughter cannot afford to give up her job to look after him A constant-attendance allowance, such as is already paid to some war pensioners, might make all the difference, and Mr Townsend proposes, as he explains in his letter on p 910, that this allowance be extended to include bedridden old-age pensioners

The strain on the family can also be eased by anything which contributes to the old person's physical and mental independence Fry [3] suggests that it is the duty of the family doctor to get to know all the old people on his list and to keep in touch with them On a larger scale, the welfare department of the city of Salford is to be commended for making its services known by giving every person reaching pensionable age a booklet which contains a reply-paid postcard for those who desire a visit The health visitor, at once a nurse and a social worker, can, by regular visits, do much to prevent that gradual deterioration in old people which goes on slowly until, in Townsend's words, "a neighbour sees a bottle of milk standing on the doorstep long after it has been delivered, makes inquiries and sends for an ambulance" Old people's clubs and unofficial friendly visiting by volunteers also preserve an interest in life and the self-respect that goes with it "Meals on wheels", a voluntary service which is well established in many towns, gives a useful boost to morale, and in a few places help with laundry has been arranged Chiropody also is important in keeping the elderly fit Finally, domiciliary physiotherapy may have a useful future, as has been shown in Belfast [6]

Townsend is right to suggest that these many services should be "closely connected with the work of family doctors" Walsh [7] has discussed the value of these services in general practice, and Fry proposes that the medical officer of health should be available for domiciliary visits as "a consultant in social medicine" Others, including apparently the Minister of Health,[8] see here one of the special functions of the geriatrician, and a good geriatric outpatient department with an almoner, physiotherapist, and occupational therapist working together, when necessary within the framework of a day hospital, will undoubtedly achieve more and more in the future

TIETZE'S DISEASE

In 1921 Tietze [9] described four cases of "swelling of costal cartilages of unknown ætiology, insidious in onset, spontaneously painful, not associated with constitutional disturbances, and of a prolonged, fluctuating course" He believed that this might be a cartilage dystrophy, possibly associated with wartime malnutrition In Britain the disorder was first noted in 1942 by Gill et al,[10] who described five cases in young soldiers and considered that symptoms and signs might be present for a very long time Histological examination of costal cartilage in one of their cases showed no departure from normal Deane [11] found that the second costal cartilage was most commonly affected, and he noted that a painful swelling at onset might be associated with a respiratory infection, the pain diminished but the swelling often remained The histological changes in biopsy specimens of costal cartilage they regarded as variants of normal They suggested that the disorder originated either in a small tear or in rheumatoid involvement of a ligament Beck and Berkheiser [12] described four cases in which the costal cartilage was exposed at operation and was found to be acutely buckled forward They suggested that this buckling was due to disease of the underlying ligament, but no specimen of ligament was taken for examination The difficulties in the differential diagnosis of this condition have been indicated by Wehrmacher [13], but there is no doubt that familiarity with the syndrome makes its recognition fairly simple

Karon et al [14] have now described thirteen new cases Their criteria of diagnosis are (1) the presence of a painful, tender mass in one or more costal cartilages, (2) evidence that the mass is a distinct enlargement, not present normally, which eventually subsides, and (3) the absence of a definite alternative ætiological diagnosis The swelling and tenderness usually make the diagnosis immediately apparent, and radiography and hæmatological investigations eliminate underlying disease of rib, lung, or heart There is no specific treatment, and in most cases reassurance and local heat and analgesics suffice Surgical excision should be unnecessary, provided the diagnosis is not in doubt Local infiltration of hydrocortisone in patients who do not respond immediately to simple measures may be expected to bring prompt relief from pain together with diminution of the swelling [15]

Prince Philip, Duke of Edinburgh, has accepted the invitation of the British Medical Association and the Canadian Medical Association to be their president for 1959–60 The associations are holding their annual meetings jointly in Edinburgh in July, 1959

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[2] Hobson W Pemberton J The Health of the Elderly at Home, p 141 London 1955

[3] Fry J *Brit med J* 1957, ii 666

[4] Wright C H Roberts L *Lancet* Feb 1, 1958, p 254

[5] Chalke, H D *Brit med J* 1957, ii 694

[6] See *Lancet*, Jan 4, 1959, p 36

[7] Walsh R C *in* Old Age in the Modern World, p 83 Edinburgh 1955

[8] H.M (57)86

[9] Tietze, A *Berl klin Wschr* 1921, 58, 829

[10] Gill A M, Jones, R A, Pollak, L *Brit med J* 1942, ii, 155

[11] Deane E H W *Lancet*, 1951 i, 683

[12] Beck, W C, Berkheiser, S *Surgery*, 1954 35, 762

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[14] Karon, E H, Achor, R W P, Janes J M *Proc Mayo Clin* 1958, 33, 45

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Symposia

TRAINING

The Betterment of Human Effort

A SYMPOSIUM arranged by the Ergonomics Research Society in Bristol on April 13–16 tackled the Problems of Training, and the discussion ranged as widely as the title suggested it would As Mr M G BENNETT, of the operational research division of British Railways, remarked, ergonomics is a funny subject for one thing, its scope is certainly very broad indeed One of the difficulties which face those engaged in the study of man in relation to his work—industrialists, psychologists, doctors of several sorts—is that there are huge practical tasks to be completed in industry and elsewhere at a time when relatively little is known about the theory of the subject. And with so many different people involved, meetings of the kind which the Ergonomics Research Society arranges are an enormous help Last week's meeting was well attended, but perhaps some groups vitally concerned were not as fully represented as they should have been At the close of the symposium, Prof R C BROWNE (Newcastle upon Tyne) said he would like to see at next year's meeting more young executives from industrial organisations, more lecturers from university departments of engineering and colleges of technology, and more young doctors from industry

The account that follows includes only some of the papers read at the symposium and we have given particular attention to the contributions with a medical content. This unbalanced picture does not therefore record many important matters concerning training for skilled employment, which occupied much of the symposium's time

TRAINING AND THE HEART

Dr M J KARVONEN (Helsinki) discussed the effects of physical training on circulatory dynamics The "trained" cardiovascular system might be said to be one in which a high cardiac output was associated with a high oxygen uptake The heart-volume was usually increased and the resting pulse-rate was often but not always slow The diffusion capacity of the lungs was closely related to the condition of training of the cardiovascular system, and diffusion capacity at rest showed a negative correlation with pulse-rate during standard exercise and with age Several pulse-rate tests had been used to assess the degree of training, and the step-test pulse-rate had been found to be closely correlated to the resting rate, the maximum rate, and the increase in rate between rest and work The heart-volume of a group of long-distance runners was round about 600 ml per sq m of body surface, for sprinters the figure was between 300 and 400 ml per sq m During a hard training season the size of an athlete's heart could increase considerably To produce a drop in the pulse-rate during standard exercise, training exercises must raise the pulse-rate above 130–140 per min Below this level, Dr Karvonen had found no training effect on the cardiovascular system, and he concluded from pulse-rates commonly observed during occupational work that such work had little training effect on heart function. The gentle trot to the station seems, therefore, of little value from this point of view it is better to leave three minutes later and go in for a full-blooded sprint

Training, it was said, made man better adapted to exercise, but, Dr Karvonen added with a twinkle, it might also be argued that lack of training made man better adapted to rest In fact the work done by the trained heart at rest was half to two-thirds less than that performed by the untrained heart The higher maximum cardiac output conferred a greater capacity for work and under certain conditions (e g, in heat and while flying under accelerating forces) this was a particular advantage

Some people said that training of the cardiovascular system was dangerous, but Dr Karvonen had no such fears At a few critical moments, a trained cardiovascular system was a distinct help Women with small hearts were more likely, it seemed, to give birth prematurely than heartier mothers, and a study of champion skiers' prospects of reaching old age showed that their insurance companies had little to worry about Dr Karvonen concluded modestly that the evidence indicated that exercise was "not acutely toxic to the organs"

TRAINING AND THE LUNGS

Dr J E COTES (Cardiff) described some investigations he had carried out with a colleague, Mr F Meade, into the effect of training on pulmonary ventilation during exercise 11 young men were studied before and three times during their National Service preliminary training course Ventilation, end tidal pCO_2, and body-temperature were measured at rest and while walking at $3^1/_2$ m p h on a motor-driven treadmill. The rate of working against gravity during the treadmill walk was calculated from the vertical oscillation of the body During the weeks of their training, the men's ventilation minute volume, total energy expenditure, and vertical work done all decreased The reduction in energy expenditure could be fully accounted for by the reduction in lift work A graph of the rate of energy expenditure against rate of lift work gave a straight line—the line of constant efficiency of conversion of chemical to mechanical energy The findings suggested that the greater part of the reduction in pulmonary ventilation with training was due to increased economy of performance There was also evidence of increased arterial oxygen tension as the result of training No change was noted during training in the ventilation equivalent for oxygen, perhaps because the work level was well below that necessary to induce anærobic metabolism Dr Cotes suggested that the men used less air in the performance of a standard task by virtue of greater economy of effort and more efficient aeration in the lungs, with a consequent increase in arterial oxygen tension

PHYSIOLOGICAL BASES OF TRAINING

Prof A HEMINGWAY (Leeds) spoke of the two main types of training the imposed disciplining of patterns of movement and the development of resources so that tasks previously impossible came within the individual's capacity If a worker was trained according to physiological postulates concerning movement and posture then he could work more economically Improvement with training came as the result of better coordination of muscles and the elimination of unnecessary movements The extension and improvement of the physiological capabilities of the individual enabled him to perform a given task with less encroachment on his reserves or with greater efficiency In artistic activities or sport, however, excellence of performance, as judged by skill, endurance, or strength, counted for more than efficiency, and training was then directed at exploiting the potentialities of the body and at the development of fitness for a task, "the growth of the wisdom of the body"

Professor Hemingway mentioned Dr Roger Bannister's views on the importance of a certain mental approach in the athlete that enabled him to endure when physical discomfort was intense, and he also illustrated some training schedules of the repetition type, involving alternate fast running and recovery phases, that many trainers now believed to be the best way of bringing a middle- or long-distance runner to peak performance

EIGHTEEN MILES A DAY

The effect of short periods of exercise, lasting a few days, on the fitness of relatively untrained young men has not been closely studied, and Dr J V G A **Durnin** (Glasgow) decided to look into the matter 44 young men in an R A F unit, who had had almost no exercise, were divided in four groups one group continued to take almost no exercise, the second walked 6 miles a day, the third 12 miles, and the fourth 18 miles over hilly country on rough tracks and metalled roads Cardiorespiratory function was measured during a standard exercise on the treadmill and these measurements were made before the beginning of training, at the end of five days' exercise, and at the end of ten days In all the marching groups, there was a significant decrease over the training period in the exercise heart-rate compared with the controls, and the 12-milers also showed a significant decrease in pulmonary ventilation and oxygen consumption In no group was the change in heart-rate 1–1½ minutes after exercise significant Perhaps the most surprising of Dr Durnin's observations was the casualty-rate from sore feet—only 2 men incapacitated for half a day each

During discussion it was asked what a high mark in the Harvard step test indicated, and one answer was "fitness to do the Harvard step test" But Dr O G **Edholm** (London) had more confidence in it as a measure of physical fitness, even though it was not ideal *

HARD WORK

Mr J G **Fletcher** (London) had found that "well-motivated" young men could increase their maximal amount of physical work very rapidly by exercising once a day to exhaustion, using a constant high rate of work The physiological changes were investigated and the rates of improvement compared in different subjects A simple work test (stepping up and down on a 22-inch bench thirty times a minute for as long as possible) was used, so that the acquisition of skill played no great part in any improvement The reactions of 10 healthy men between 20 and 46 were studied At first men in poor shape could continue stepping for only about a minute, but a cross-country runner was able to carry on for 35 minutes Endurance improved rapidly with repetition, and 3 non-athletes achieved 15 minutes An ex-athlete and swimmer got up to 30 minutes from a poor start in only 8 attempts, an Antarctic explorer took about twice as many attempts to get up to 15 minutes, and a sedentary worker reached 15 minutes only after about 30 attempts The resting heart-rate was lower after training than before it, and recovery rate after work was more rapid Those people who were retested after an interval without training all retained some improvement Mr Fletcher concluded that in this type of exercise maximal output could be much increased provided (and there was the rub) "subjects are prepared to work to exhaustion"

INCREASING MUSCULAR STRENGTH

Prof E A **Muller** (Dortmund) looked on a muscular contraction as having two different effects—one preventing atrophy and the other increasing strength Atrophy, he had found, was prevented by one short static contraction daily of at least 20% of the maximal strength At least one short static contraction a week of 35% maximal strength was needed to ensure increase in the strength of a muscle Muscular strength could be increased much more rapidly by daily contractions, but the benefit was lost correspondingly quickly after "training" was stopped Professor Muller and his colleagues at the Max-Planck-Institut fur Arbeitsphysiologie had found, however, that there was nothing to be gained by increasing the training stimulus by stepping up the daily number, duration, or force of the contractions Strength reached by quick training could be kept undiminished by one contraction a fortnight, and maintained in that way for several weeks, it would then persist without further training

NOISE AND TRAINING

Mr D E **Broadbent** (Cambridge) had been investigating the effects of noise early in training upon subsequent performance The design of previous experiments had divided the subjects in such a way that half learned a task in quiet conditions and half in noise The environments were then reversed and the effect on performance noted In general it was found that those who had learned the task in quiet performed better during the second session—in other words, and not unexpectedly, the conditions under which a man first met a task affected his subsequent performance when conditions improved In several experiments it was noted that the subjects learning in noise did badly throughout the experiment, including their subsequent performance in quiet These experiments were not entirely satisfactory in that there were only two groups (noise→quiet, and quiet→noise), so that the findings could have been accounted for if a practised task was done better in noise than in quiet Mr Broadbent, therefore, added a third group (quiet→quiet) and repeated the experiment The subjects memorised a six-figure number shown to them the number was concealed, a four-figure number displayed, and the subjects had to subtract one from the other in their heads The time they took for each problem was taken as the measure of efficiency At the first session of tests the two groups in quiet improved their times, but the group in noise got worse At the second session, after the first two groups had reversed their environments, the noise→quiet group again deteriorated considerably, while the quiet→noise subjects maintained their efficiency (as judged by time per problem) almost unimpaired, and the quiet→quiet competitors went on improving happily These findings emphasised the importance of paying as much attention to the environment of workers in training as to that of workers in the production line

PRACTICE MAKES IMPERFECT?

Dr O **Graf** (Dortmund) reported some more interesting work at the Max-Planck-Institut In two experiments with 4 female workers spaced practice (4 fifteen-minute spells daily) at an operation for punching holes in cards was compared with continuous practice (eight hours daily) The striking finding was that spaced practice over a period of fourteen days produced surer movements and faster work than continuous practice spread over four months Other types of work studied in this way were bradawling and riveting The influence of fatigue in continuous practice might, Dr Graf suggested, lead to the development and retention of incorrect movements which slowed down the operation

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* In a letter on p 912 a correspondent refers to variations in the technique of performing this test —Ed L

SKILL AND NATURAL SELECTION

Imagine a learner, suggested Dr E R F W **CROSSMAN** (Reading), with a repertoire of different methods for doing the job he is learning, each method with its own probability (strength) and time If the methods taking longer were negatively selected, many methods would increase in strength Laboratory and industrial observations with element-by-element recording apparatus had shown that the speed of an operation increased through a change in the shape of the frequency-distribution of element-times rather than from a bodily shift in its position These and other findings suggested that skill was acquired by the unconscious selection of appropriate methods from an initially random assortment Selection must depend on something more than conscious knowledge of results—perhaps on unconscious perception of the time taken by each element More likely, however, Dr Crossman thought, was the unconscious selection by the operator of those methods which required least work on his part, so that increased speed was secondary to reduced effort

CASES AND PAVING-STONES

Dr F H **BONJER** (Leyden) had measured energy expenditure, pulse-rate, working time, and amount of work performed during certain jobs Various methods of handling cases while stowing them in the hold of a ship had given the following results

	Tilting on long edges	*Tilting on short edges*	*Tilting on edges with hook*	*Tilting on angular points*
Energy expended (kg-cal. per case)	2 2	2 5	2 2	1 2
Heart-beats per case	135	136	152	123
Work done (kg-m per case)	111 3	107 6	107 6	71·4

The best method, judged by these figures, was to manhandle the case on its points, and Dr Bonjer showed diagrams to illustrate that workers using his method were able to keep a more upright posture than those using other methods

Dutch paving-stone layers are divided into three schools—standers, sitters, and kneelers—and Dr Bonjer produced a film to show how each school worked The sitters had a little one-legged stool, which looked uncomfortable, and the kneelers seemed none too happy either, on appearances the standers certainly had it But both standers and sitters, it was found, were laying about 20 stones a minute for the same rate of energy expenditure, and kneelers in the Hague could do just as well, though elsewhere kneelers' rate of laying was not so good But the kneelers had the champion on their side, a remarkable performer who came from a well-known family of pavers and who put down 30 stones a minute These investigations demonstrated the complexities that individual variations could introduce into a group study

PROCRUSTES AND THE WORKING MAN

Procrustes was a fabulous robber of Attica who made his victims conform to the length of his bed by stretching or mutilation, and Dr F V **TAYLOR**, of the U S Naval Research Laboratory, Washington, introduced what he called a " cacophonous note " with a sprightly attack on the " procrustean approach to the optimisation of man-machine systems " Is it better to adjust the human component to the requirements of the system (as Procrustes did) or to enhance system performance by adjusting the mechanical elements to fit the man? Dr Taylor announced unashamedly that he proposed to arrange his data (which could be made to support either approach) so that Procrustes would lose And lose he apparently did For example, in an experiment with operators learning to use two tracking systems (one with a simply learned position control and the other with a harder-to-master acceleration control), training could make the operators of the acceleration control as efficient as those using the simpler device, but they reverted to their original order of merit when the operators were subjected to any one of a wide variety of " task-induced stress situations " Stress disrupted most readily the system which put most dependence on the man, and the procrustean approach might therefore obscure important operational deficiencies of a man-machine system

VENEREAL DISEASES

A W H O seminar on venereal diseases was held in Tokyo on March 17–29, under the presidency of Dr M **YAMAGUCHI** Information was exchanged about venereal disease in the Western Pacific region of W H O

It is evident that in many countries syphilis has declined since 1945 No evidence of widespread endemic non-venereal syphilis was forthcoming, though cases were reported from French Polynesia Yaws is, however, a problem in Laos, Malaya, the Philippines, and the Pacific Islands In general syphilis is being well controlled with penicillin

Gonorrhœa, on the other hand, after a post-war fall is again increasing in many areas, and is not responding to repository penicillin as well as previously Failure-rates of up to 30% are being noted on higher doses than those giving 95% success only a few years ago The gonococcus seems to be becoming less sensitive to penicillin Whether this is because the organism has developed new metabolic processes or, as seems more likely, because of repeated selection of less sensitive strains is not definitely known The need seems to be to provide higher peaks of blood-penicillin by means of shorter-acting penicillin Such preparations lack one advantage of repository penicillins—the long period of penicillinæmia during which the consorts can be secured for treatment before the patient becomes reinfected Mixed preparations containing both short- and long-acting penicillins may provide the answer, but the situation is disquieting

Non-gonococcal urethritis is emerging as diagnostic facilities for gonorrhœa improve It is commoner than gonorrhœa in some Japanese clinics Of the other venereal diseases, chancroid is thought to be the most important, especially where provision for dark-field examination is inadequate In some countries chancroid is several times commoner than primary syphilis, and, if no dark-field examinations are made, cases of chancroid with positive serological tests (due to late latent syphilis or to past yaws) will be unfairly classified as penicillin failures when—as is likely—the tests fail to reverse

It was agreed that there is much more venereal disease in the area than has been reported in the official returns Special one-day surveys in Japan have indicated that 6–10 times the number of cases actually reported may be present

PENICILLIN REACTIONS

Fatalities from penicillin reactions have caused alarm in some countries—notably Taiwan, where some 17 deaths have been reported All countries have experienced deaths from penicillin anaphylaxis which, because patients die in the doctor's consulting-room rather than in hospital, attract attention and publicity Penicillin anaphylaxis is commoner after intravenous than after intramuscular injections, and after any injection than after oral administration. Reactions are thus commoner with the more quickly absorbed preparations, which are those most used in general practice They are much less common in venereal-disease clinics, where repository penicillins are used In a recent W H O survey of over 600,000 patients, there was only 1 death from penicillin in 70,000 treated, and in the W H O -assisted venereal-disease-control programme in Taiwan there was only 1 death in 44,000 treated

Many of the severe reactions have arisen in persons with a previous history of allergy, especially to penicillin It was suggested that many fatalities can be avoided if a careful preliminary history is taken Important in the prevention of such reactions is the restriction of the use of the drug to only well-established indications and of its sale to the production of a doctor's prescription (antibiotics may be bought over the counter in many countries of the Western Pacific region) Some deaths can be prevented by resuscitating drugs, and all doctors who administer penicillin should have on hand an emergency kit containing appropriate syringes, adrenaline, nikethamide, hydrocortisone, an anti-histamine drug for injection, aminophylline, and, if available, penicillinase

LIVER DISEASES

A SYMPOSIUM on liver diseases was held in Lund and Malmo, Sweden, on March 28 and 29, under the joint presidency of Prof J P SANDBLOM and Prof J WALDENSTROM

Dr H VETTER (Austria) described the use of radioactive colloid materials in the estimation of liver blood-flow This is based on the assumption that these substances are removed from the circulating blood by the cells of the reticulo-endothelial system, which are mostly found in the liver This removal is estimated by simply placing a counter between the thighs Suitable radioactive substances are colloidal radiogold and heat-denatured human serum-albumin labelled with ^{131}I In cirrhosis of the liver, comparison of results obtained with colloidal radiogold with those for bromsulphalein showed that two-thirds of the diminished bromsulphalein removal was due to decreased liver blood-flow and not to impaired liver-cell function There was a significant negative correlation between the liver blood-flow and the portal venous pressure

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Dr R L BLOMSTRAND (Sweden) had cannulated the thoracic duct and studied the lymph biochemically 10–50% of the thoracic-duct flow comes from the liver The normal flow was 40–120 ml an hour A patient with cirrhosis produced 500 ml an hour This overproduction would support the hypothesis that ascites is produced from liver lymph Erythrocytes injected into the ascites could be recovered from thoracic-duct lymph

Dr C E EKMAN and Professor SANDBLOM reported their results for portocaval anastomosis in cirrhotic patients with portal hypertension 11 of 69 patients died after operation Preoperative tests showed that 9 of those dying had poor liver function and 2 good liver function This emphasised the importance of reserving this operation for those with good hepatic reserve 42 of 55 survived one year and only 2 had further gastrointestinal hæmorrhage

Dr H KROOK (Sweden) had used the occluded (wedged) hepatic vein technique to measure the portal venous pressure A raised pressure was diagnostic of cirrhosis The presence of vascular spiders correlated with the height of the portal venous pressure

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Dr F SERIN (Sweden) reported a patient with mushroom (*Amanita virosa*) poisoning A period of hepatic failure followed the initial diarrhœa and vomiting, and this was marked by jaundice and a rise in the serum-enzymes aldolase, glutamic oxaloacetic and glutamic pyruvic transaminase, and malic and lactic dehydrogenase These were presumably released by the damaged liver Disturbances in blood coagulation were shown by a fall in Christmas factor and factor V, antihæmophilic globulin was unaffected, and was probably not of hepatic origin

Professor WALDENSTRÖM commented on the group of adolescent patients, with cirrhosis, acne, and high erythrocyte-sedimentation rates, that he originally described in 1950 Jaundice might not be present, and such a patient with predominant portal hypertension had benefited by portocaval anastomosis Dr S SHERLOCK (Britain) had noted that these patients often showed an excessive adolescent growth spurt Dr G H JEFFRIES (Britain) had seen steatorrhœa, which did not seem to be of pancreatic or intestinal origin, and might be due to diminished hepatic production of bile salts

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QUANTITATIVE METHODS IN HUMAN PHARMACOLOGY

A SYMPOSIUM on Quantitative Methods in Human Pharmacology and Therapeutics, arranged by the Coordinating Committee for Symposia on Drugs and supported by the British Pharmacological Society, the Physiological Society, the Royal Society of Medicine, and the Biometric and Nutrition Societies, was held in London on March 24 and 25

Sir CHARLES HARINGTON remarked that it had been said that the invasion of biology by mathematics had robbed it of much of its charm But the quantitative aspects of biology were vitally important, and those who, like himself, hankered after the days when workers could be content with qualitative observations had to recognise that this feeling was a weakness to be sternly suppressed

Quantitative studies gave new information at laboratory and clinical levels They were vital for effective therapeutics

Prof J H Gaddum pointed out that the advance of the science of therapeutics was due not only to the provision of new drugs but also to the methods of measuring their effects—which was, for the first time, to be the theme of a symposium Although there was no effective remedy for the common cold we had at least learnt how to prove that certain remedies were less effective than some people supposed He hoped that nobody would stay away from the session on statistics because they might think it likely to be too difficult He said (to the evident relief of many present) that there was no need for doctors to understand statistics but it was important for them to know what statistics could and could not do for them

OBJECTIVE ASSESSMENT

Dr Harry Gold described problems of measurement in his experience of assessing in patients the effects of xanthine derivatives and khellin on angina pectoris, and of digitalis It was essential, when subjective judgments were being made, that not only the patient but also the doctor should be kept in ignorance of the treatment used Doctors, he said, had little difficulty in accepting the power of suggestion as applied to their patients, but the notion that the same applied to the doctor had not had an equally cordial reception Experimental therapeutics had come to depend on the development of accurate pharmacological techniques in man, there was no escape from it Resistance to the idea that exact measurements were needed still existed, however, it was due to faulty thinking

METHODS OF EVALUATION

Prof C A Keele described the measurement of analgesia in man He declined to define " pain ", remarking that it was an experience we could all recognise easily enough Measurement of pain indirectly by means of the observable concomitants (sweating, wincing, changes in heart-rate, &c) had not been as satisfactory as simple subjective assessment He proposed an index obtained by multiplying the pain-relief score by the side-effects score, calling this the " score of contentment ", which would enable the therapeutic usefulness of drugs to be compared conveniently

Dr Peter Sainsbury discussed the measurement of bodily changes accompanying emotion Measurement of muscle tone and involuntary movements was practicable with minimal disturbance of the patient, and it could be reasonably quantitative He was able to measure the amount of gesture, fidgeting, and tie-adjusting, as well as muscle-tone, and to record the effects of drugs on these

Dr H Steinberg described the measurement of the effects of drugs on various kinds of performance—reasoning, association and memory, perception and vigilance, and motor coordination and speed Complex intellectual performance had been little studied quantitatively, probably because of the difficulties, but interesting results were being obtained It had been shown, for example, that drugs might reduce performance in a test by reducing incentive and not by interfering with ability to perform During intellectual tests knowledge of results could act as a spur, and the effects of some drugs had been shown to differ according to whether or not this spur was present Small amounts of anxiety acted, as expected, as an incentive to performance, but large amounts were incapacitating The effects of drugs on these factors could now be measured

Prof L Goldberg described how it is possible to measure the effects of drugs on motor activity and stability He instanced an experiment in which Romberg's test was performed with a light attached to the subject, the movement of which was recorded on a photographic plate

Dr H K Beecher discussed the measurement of subjective states He suggested that pharmacologists did not play a large enough part in experimental therapeutics, remaining detached from the clinic, which was too far beneath their ivory towers for them to notice it He thought (and the meeting obviously agreed) that the accurate measurement of subjective states was one of the most important advances in experimental therapeutics

STATISTICAL METHODS

Dr W G Cochran lucidly described the use of such techniques as Latin squares, randomised blocks, and sequential analysis, and their merits in assessing responses to drugs Dr C C Spicer discussed the statistical treatment of results when these could only be assessed semiquantitatively by grading into pluses and minuses by the observer Such a method could be accurate and reproducible Dr D J Finney asked whether the habit of expressing doses of drug as weight per kilogramme of body-weight was entirely satisfactory in the light of new statistical and pharmacological practice There was some discussion, but he remained unanswered

CLINICAL TRIALS

Prof A Bradford Hill said that it was just as well that the newer statistical techniques, which were so valuable for extracting the maximum amount of information from data, had not been available ten years ago, when the scientific basis of therapeutic trials was being established, for it was doubtful whether clinicians would have tolerated them Now, however, with the principles of clinical trials widely accepted, it was possible to introduce newer techniques, such as sequential analysis, without astonishing physicians too much

Prof W A Bain discussed the design of small-scale drug trials and pointed out that with careful design a great deal of valuable information could often be obtained from a very few patients Since subjects for clinical trials of new drugs might be very scarce it was vitally important to attend carefully to design if many drugs were to be tested at all

Dr Richard Doll discussed some practical problems of the design of clinical trials—in particular the necessity for controls, including the use of dummy drugs Randomisation was important, allotting of patients or treatments alternately had serious disadvantages

Finally, Dr T F Fox spoke on the ethics of experiments on man

He pointed out that patients must be able to rely on a doctor doing what was best for *them*—not what he thought best for other clients, or for himself, or for his profession, or for science On the other hand, to deserve the trust of the public, doctors must have knowledge, and their duty to advance knowledge could not be fulfilled without clinical experiment A clear distinction must be drawn between the sick person as patient (to whom nothing must be done except to his direct advantage) and the sick person as volunteer (a legitimate object of experiment) This change of status required the person's consent If, before entering hospital, patients had read a printed explanation mentioning the need for experimentation, perhaps they could be regarded as having given implicit consent for penicillins are used In a recent W H O survey of over 600,000 patients, there was only 1 death from penicillin in 70,000 treated, and in the W H O -assisted venereal-disease-control programme in Taiwan there was only 1 death in 44,000 treated

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Sir Charles Harington remarked that it had been said that the invasion of biology by mathematics had robbed it of much of its charm But the quantitative aspects of biology were vitally important, and those who, like himself, hankered after the days when workers could be content with qualitative observations had to recognise that this feeling was a weakness to be sternly suppressed sanctity of human life man comes from the earth and will return to it as though he had never been, and he has no rights beyond these which the State confers on him It is at least logical that if man exists for the State, the State has the right to do whatever is expedient with him It is not illogical for Lenin to write "Three-quarters of mankind must die if necessary, to ensure the other quarter for Communism" Such an ethic has foundations in basic beliefs about the nature of man—however untrue those beliefs may be

What a difference from humanism! The contrast lies in humanism's high estimate of man. Its aim is to gain the greatest development for every human being, and this by education, not by force Much of the noblest effort and achievement, such as liberal education and modern democracy, has sprung from this exalted view And yet these two, Communism and humanism, are alike in one major aspect they both deny the supernatural and God In denying God, humanism builds its ethics on sand "Ought" and "ought not" are words that have real content and meaning only for those who recognise an Authority who can make absolute demands on them The "ought" of humanism is the consensus of humanitarian opinion, the sanction of expediency and public taste We are not ignorant of the force of propaganda and indoctrination to change these standards—and to rationalise the change In this lies the danger of accepting our clinical ethics from the borrowed capital of humanism

If one doubts the possibility of our ethics being changed by circumstances, and those changes being accepted by medical and other humanitarian people, one has only to consider Germany in our own time This sad example shows how our accepted standards can be lost if we hold them loosely and without adequate reason. As T S Eliot has said, "If you remove from the word 'human' all that belief in the supernatural has given to man, you can view him finally as no more than an extremely clever, adaptable and mischievous little animal" In spite of humanism's high estimate of man, the inhumanity of man to man has never been more obvious than it is to this generation

The shallowness of some contemporary writing on medical ethics, said Mr Jackson, is the failure to follow through to basic concepts of the nature of God and man Our accepted ethics of clinical research are of Christian origin, being based on the nature of man and the value of his life in God's sight. The extent and growth of totalitarian ideologies make it clear that we cannot assume that our present standards are either self-evident or unlikely to be assailed There is no safety in standing on "the uncertain sands of past traditions, or that ever-changing contemporary belief—the consensus of humanitarian opinion"

SENIOR REGISTRARS

Correspondence between Minister of Health and Chairman of Joint Consultants Committee

The Joint Consultants Committee and representatives of the Ministry of Health have been jointly considering the future of the time-expired senior registrars The Joint Committee found themselves unable to agree to proposals put forward by the Ministry, and asked to see the Minister of Health. The planning subcommittee of the Joint Committee, led by Sir Russell Brain, met the Minister on March 25 In the course of a full discussion the Minister said, among other things, that present economic conditions obviously made it difficult to contemplate any substantial increase in the consultant establishment. The Joint Committee, later the same day, considered the result of this meeting and asked Sir Russell Brain to see the Minister again for further discussions Sir Russell met the Minister on April 1, and the Minister promised to comment in writing on the views of the Joint Committee Subsequently the following letters were exchanged

9th April, 1958

Dear Sir Russell,

When we had our talk about senior registrars on the 1st April I said I would write to you on the points you raised and let you know the lines of the statement I am proposing to make to Parliament after the Recess

You told me that the Joint Committee were not happy about the creation of a new grade which would consist of people some of whom might not become consultants From this it appears that I cannot have made my proposals quite clear I know the Committee's views about the creation of a new grade, and though I do not share them, my proposals are deliberately drawn to deal with the immediate problem of the time-expired senior registrars in a reasonable way without raising the contentious issue of a new grade

The whole plan of the draft circular put to the Committee last year was to make reasonable provision for these time-expired men in senior registrar posts, not in posts of some new grade The fact that the extended salary scale envisaged by the draft circular would be attached to a limited number of senior registrar posts, not to all, does not conflict with that concept At the same time the plan avoids the difficulty presented by the suggestion that has been made that all senior registrars who do not obtain a higher appointment within their normal term of training or within a defined period of its completion should automatically become entitled to a higher salary As I explained in the course of our conversation, an arrangement of this kind would be a simple inflationary salary increase and not consonant with the Government's policy Moreover, it would be wrong to change the salary scale for senior registrar posts generally while the Royal Commission is in the midst of its enquiry into remuneration

Similar considerations stand in the way of arranging that all senior registrars who fail to secure a consultant post within a reasonable time would be put in the senior hospital medical officer grade If, however, the proposition were that the designated posts envisaged by the draft circular should be in the senior hospital medical officer grade instead of in the senior registrar grade the same difficulties would not apply—though, as you said, there might well be others Before I could say whether such a proposition would be acceptable I should need to be given fairly full details, including information of the modifications which would be proposed to the agreement of 1950 on senior hospital medical officer posts For the time being, therefore, I think we should keep to the idea of making suitable provision in senior registrar posts

The suggestion that senior registrars who were doing consultant work might forthwith be given consultant status but not the pay of consultants, and be assured that they would be given a consultant appointment when economic and other circumstances allowed, does not seem to me to offer an acceptable solution to the difficulty and I should have expected that this applied from the Joint Committee's angle just as much as from mine We do not want the posts occupied by these time-expired senior registrars to be regarded as a substitute for additional consultant posts This is stressed in the draft circular What we have in mind, as I have said, is that they would still occupy posts which entail work proper to the senior registrar grade, and designated posts involving work commensurate with that which is normally expected of a fourth year senior registrar would carry the extended salary scale The holders would be able to continue to compete for consultant vacancies and no doubt they would do so This is now the established method of obtaining consultant status, and I am sure that it is the method that serves the best interests of the hospital service—which must be the paramount consideration—and must be maintained intact for that reason minor procedures carrying virtually no risk and causing little discomfort. But, even so, the decision about these procedures should be taken by the doctor who had undertaken to look after the patient and therefore to put his interests first (called by Guttentag the " physician-friend "). When an experiment was more than trivial, the " physician-experimenter " (whose chief concern was to solve a problem) should be a different person from the physician-friend, and the consent must be explicit not implicit. It must also be valid, and, if the patient could not understand what was proposed, supplementary consent should be obtained from a medical person acting on his behalf, preferably his family doctor.

In the discussion one or two speakers regarded it as impracticable and undesirable to separate " experimenter " and " friend " the patient, they felt, was best safeguarded if the experimenter was personally and fully responsible to his patient. Dr Fox, however, thought that the vision of investigators, when engaged in experiments, was liable to become so concentrated and limited that they could not suitably take decisions on the patient's behalf. Decisions could be very difficult, and, if an experiment was doubtfully justifiable, the experimenter could properly be questioned by his peers when he reported his work to a society. Medical journals, too, might properly ask authors to include specific assurances that the patients were true volunteers, and it was professionally healthy that clinical experiments should occasionally be challenged publicly by those who found them disturbing.

Dr J van Noordwijk gave an account of an official Dutch study of the ethics of human experimentation. Several workers explained their experiments, and invited Dr Fox to comment on their ethical position—which, as an outsider, he declined to do. The questions showed that clinical workers are conscious of the perennial difficulties facing those who try to advance knowledge by working on man.

The proceedings of the symposium are to be published by the Pergamon Press, London.

Special Articles

MORAL RESPONSIBILITY IN CLINICAL RESEARCH

Mr D MacG Jackson, surgeon to the Birmingham Accident Hospital, spoke on this subject at a London meeting of the Christian Medical Fellowship on March 26.

Research, he said, is a new departure in medicine, with the future in mind there is no reference to it in the Hippocratic Oath. It may take the form of " observation " or " planned experiment ", or both, but experiment is a sharper tool—it has been compared to cross-examining Nature rather than merely overhearing her. Though experimental clinical research will probably always remain the call of a few, these should have the fullest understanding and willing cooperation of their clinical colleagues, because research is a moral responsibility of all doctors. As McCance has remarked, without continued research our knowledge would fall away as it did in the Middle Ages and be forgotten. For those who have qualms about the value and propriety of clinical research, the answer to inhuman research is humane research—not no research at all.

The greatest interest in the morality of clinical research is shown by the public, who realise the importance of interpersonal relationships with doctors. In practising clinical research there is an obvious conflict of loyalties which is not shared in purely medical work. The physician's care is focused first, last, and all the time on his patients, but the good investigator must be very much interested in his problem. There are many other loyalties, however, common to both these men, which conflict with that to their patients—responsibilities for teaching, for their families, for their livelihood, their own health and recreation, and perhaps for Christian, social, or political work. The investigator has just one more loyalty to which he must give correct priority—loyalty to his particular search for the truth.

F H K Green has pointed out that " when the value of a treatment, new or old, is doubtful, there may be a higher moral obligation to test it critically than to continue to prescribe it year-in-year-out with the support merely of custom or of wishful thinking. In this sort of test there are few limiting moral considerations, for it is indicated only when both of two (or more) treatments are unevaluated. Moreover, frequently there will be no indication to get the patient's permission for inclusion in such a trial. Again, various clinical " experiments "—such as taking a few extra millilitres of blood at the time of a diagnostic or therapeutic venepuncture—are not uncommonly done without obtaining permission. This is done and accepted in the spirit of good faith embodied in the doctor-patient relationship. But if the experiment is more elaborate, involving any degree of extra discomfort, risk, or cooperation, most investigators would agree that the whole procedure should be explained to the patient or parent honestly and fully, and their permission obtained. At the same time, explanation is often difficult, and because of the patient's trust in the doctor he may agree to almost anything. Hence consent, though it should be obtained, is not enough. The responsibility for an experiment rests squarely on the investigator and each member of his team at all times, and if there is any doubt the value and propriety of the trial should be considered by informed and independent opinions.

Remarking that the real difficulty lies in the application of our principles, Mr Jackson devoted the closing part of his address to " a much more neglected aspect of this subject "—namely, the source of the accepted moral responsibilities of clinicians.

The underlying concepts are, first, a belief in the sanctity of human life, and secondly a belief that the claims of the individual come before those of the society in which he lives. What is the source of these concepts? Are we still prepared to accept them, and if so, why?

The Greek world showed neither compassion nor organised care for the weak, the disabled or the hopeless case. In India, Hinduism is fundamentally a philosophy of denial of this world and life, and till recently there was no active expression of love and compassion to those in need. The earliest Buddhist hospitals in India preceded by some 400 years the first Christian hospitals, for Buddha advocated merciful action to those suffering. But, though kindness is at the centre of Buddhism, a sick man is not of value as a personality. Kindness is for the benefit of the doer rather than the sufferer, and a man's first and chief occupation is with his own redemption. In China the height of medical development was reached about the same time as that in India, but under the influence of Confucius subjection to authority produced a fatal inertia which turned tradition into a prison.

The Christian view of man is in contrast to these, and is based on the two teachings of the *Old Testament* that man is a creature created by God, and that man is made in the image of God. Linked with these two ideas is the appreciation of man as an individual each individual is unique. In contrast to the indifferent and fatalistic view of suffering reflected in Greek and Roman and in Eastern religions, Christ gave us a new estimate of the value of human life and personality. In no other religion are these basic values found, though the fruits of them are coveted and copied.

Many would accept our medical ethics as self-evidently good, while divorcing them from their foundation principles. But this is a dangerous and superficial attitude. If we feel that our present clinical ethical code is the best, it is short-sighted, if not madness, to regard it as self-evident. It is not so regarded by believers in Marxist ideology which is extending its influence now over one-third of the population of the world. Marxian Communism denies the existence of God and the sanctity of human life: man comes from the earth and will return to it as though he had never been, and he has no rights beyond these which the State confers on him. It is at least logical that if man exists for the State, the State has the right to do whatever is expedient with him. It is not illogical for Lenin to write "Three-quarters of mankind must die if necessary, to ensure the other quarter for Communism." Such an ethic has foundations in basic beliefs about the nature of man—however untrue those beliefs may be.

What a difference from humanism! The contrast lies in humanism's high estimate of man. Its aim is to gain the greatest development for every human being, and this by education, not by force. Much of the noblest effort and achievement, such as liberal education and modern democracy, has sprung from this exalted view. And yet these two, Communism and humanism, are alike in one major aspect: they both deny the supernatural and God. In denying God, humanism builds its ethics on sand. "Ought" and "ought not" are words that have real content and meaning only for those who recognise an Authority who can make absolute demands on them. The "ought" of humanism is the consensus of humanitarian opinion, the sanction of expediency and public taste. We are not ignorant of the force of propaganda and indoctrination to change these standards—and to rationalise the change. In this lies the danger of accepting our clinical ethics from the borrowed capital of humanism.

If one doubts the possibility of our ethics being changed by circumstances, and those changes being accepted by medical and other humanitarian people, one has only to consider Germany in our own time. This sad example shows how our accepted standards can be lost if we hold them loosely and without adequate reason. As T. S. Eliot has said, "If you remove from the word 'human' all that belief in the supernatural has given to man, you can view him finally as no more than an extremely clever, adaptable and mischievous little animal." In spite of humanism's high estimate of man, the inhumanity of man to man has never been more obvious than *it is to this generation.*

The shallowness of some contemporary writing on medical ethics, said Mr. Jackson, is the failure to follow through to basic concepts of the nature of God and man. Our accepted ethics of clinical research are of Christian origin, being based on the nature of man and the value of his life in God's sight. The extent and growth of totalitarian ideologies make it clear that we cannot assume that our present standards are either self-evident or unlikely to be assailed. There is no safety in standing on "the uncertain sands of past traditions, or that ever-changing contemporary belief—the consensus of humanitarian opinion."

SENIOR REGISTRARS

Correspondence between Minister of Health and Chairman of Joint Consultants Committee

THE Joint Consultants Committee and representatives of the Ministry of Health have been jointly considering the future of the time-expired senior registrars. The Joint Committee found themselves unable to agree to proposals put forward by the Ministry, and asked to see the Minister of Health. The planning subcommittee of the Joint Committee, led by Sir Russell Brain, met the Minister on March 25. In the course of a full discussion the Minister said, among other things, that present economic conditions obviously made it difficult to contemplate any substantial increase in the consultant establishment. The Joint Committee, later the same day, considered the result of this meeting and asked Sir Russell Brain to see the Minister again for further discussions. Sir Russell met the Minister on April 1, and the Minister promised to comment in writing on the views of the Joint Committee. Subsequently the following letters were exchanged.

9th April, 1958.

Dear Sir Russell,

When we had our talk about senior registrars on the 1st April I said I would write to you on the points you raised and let you know the lines of the statement I am proposing to make to Parliament after the Recess.

You told me that the Joint Committee were not happy about the creation of a new grade which would consist of people some of whom might not become consultants. From this it appears that I cannot have made my proposals quite clear. I know the Committee's views about the creation of a new grade, and though I do not share them, my proposals are deliberately drawn to deal with the immediate problem of the time-expired senior registrars in a reasonable way without raising the contentious issue of a new grade.

The whole plan of the draft circular put to the Committee last year was to make reasonable provision for these time-expired men in senior registrar posts, not in posts of some new grade. The fact that the extended salary scale envisaged by the draft circular would be attached to a limited number of senior registrar posts, not to all, does not conflict with that concept. At the same time the plan avoids the difficulty presented by the suggestion that has been made that all senior registrars who do not obtain a higher appointment within their normal term of training or within a defined period of its completion should automatically become entitled to a higher salary. As I explained in the course of our conversation, an arrangement of this kind would be a simple inflationary salary increase and not consonant with the Government's policy. Moreover, it would be wrong to change the salary scale for senior registrar posts generally while the Royal Commission is in the midst of its enquiry into remuneration.

Similar considerations stand in the way of arranging that all senior registrars who fail to secure a consultant post within a reasonable time would be put in the senior hospital medical officer grade. If, however, the proposition were that the designated posts envisaged by the draft circular should be in the senior hospital medical officer grade instead of in the senior registrar grade the same difficulties would not apply—though, as you said, there might well be others. Before I could say whether such a proposition would be acceptable I should need to be given fairly full details, including information of the modifications which would be proposed to the agreement of 1950 on senior hospital medical officer posts. For the time being, therefore, I think we should keep to the idea of making suitable provision in senior registrar posts.

The suggestion that senior registrars who were doing consultant work might forthwith be given consultant status but not the pay of consultants, and be assured that they would be given a consultant appointment when economic and other circumstances allowed, does not seem to me to offer an acceptable solution to the difficulty and I should have expected that this applied from the Joint Committee's angle just as much as from mine. We do not want the posts occupied by these time-expired senior registrars to be regarded as a substitute for additional consultant posts. This is stressed in the draft circular. What we have in mind, as I have said, is that they would still occupy posts which entail work proper to the senior registrar grade, and designated posts involving work commensurate with that which is normally expected of a fourth year senior registrar would carry the extended salary scale. The holders would be able to continue to compete for consultant vacancies and no doubt they would do so. This is now the established method of obtaining consultant status, and I am sure that it is the method that serves the best interests of the hospital service—which must be the paramount consideration—and must be maintained intact for that reason.

and also in fairness to other potential competitors for consultant posts

The terms and conditions of service do not exclude the possibility of a hospital doctor holding a part-time consultant appointment and a part-time senior registrar appointment at the same time and indeed instances exist, though they are few, of doctors holding part-time appointments in the senior registrar grade and in another grade at the same time Any extension of arrangements of this kind would depend on Boards splitting sessions which they would otherwise group for one consultant appointment and assumes that geographical considerations are no impediment This would make for administrative complication and would increase expense For these reasons I do not think that it would be appropriate positively to encourage the growth of this kind of arrangement, certainly not in advance of the Working Party's report

My general approach to the problem of the time-expired senior registrars is that we should set up a Working Party to study, in the light of experience of the hospital service since 1948, and of all other relevant considerations, the principles on which the medical staffing structure in the hospital service should be organised, and that pending the Working Party's report we should make reasonable provision for the time-expired men I am not seeking to bring about some permanent change in the staffing structure by these interim arrangements I fully accept that the arrangements should be regarded by both sides as of an interim nature pending decisions on the Working Party's recommendations, and I hope that with this explicit assurance the Joint Committee may feel able to accept in principle the suggestions set out in the draft circular for dealing with the immediate problem The way will then be clear for the details of the circular to be settled, and for the Working Party to be got under way

As you know I am committed to making a statement to Parliament immediately after the Recess The enclosed note shows what I have in mind Settlement of its final terms must await the outcome of your meeting on the 16th No doubt I shall be hearing from you as soon as the meeting is over? I think the Members who are taking a special interest in this will be counting on my making a statement on the 21st

Yours sincerely,
DEREK WALKER-SMITH

16th April, 1958

Dear Minister,

The Joint Consultants Committee has considered the discussion which some of its members had with you on March 25th and your letter to me dated 9th April, 1958 The Committee welcomes your proposal of a joint working party with the Ministry to study, in the light of experience of the hospital service since 1948 and of all other relevant considerations, the principles on which the medical staffing structure in the hospital service should be organised A recent answer which you gave to a question in the House of Commons shows what a wide discrepancy there is in the consultant establishments in certain specialties between different regions It seems to us therefore necessary to enquire how this has come about and whether the needs of the service for consultants are being fulfilled Such an enquiry by the proposed Working Party would call for a survey for this purpose We have long thought that the work done by S H M O s is in need of review and the Working Party should, and we understand would, include in its scope the consideration of the work of S H M O s, including the points which Whitley Committee B recently decided to investigate

With regard to the time-expired senior registrars we believe on a number of grounds that the only satisfactory solution of this urgent problem is that these doctors, who have long completed their training for consultant posts, should obtain such posts, but the establishment of new consultant posts must of course be related to the needs of the service, which the Working Party is to consider It seems to us more logical and practical to await the recommendations of the Working Party, which we hope will be available within a year, than at once to create new senior registrar posts which, carrying the implication that they may be permanent, are likely to prove equally unattractive to senior registrars and to hospital management committees If there should ultimately be some of the present time-expired senior registrars who do not in the end obtain consultant posts we accept the principle that such people should, if they wish, be given permanent security in the Health Service This principle being accepted, we think that the kind of work they should do needs most careful consideration by the Working Party and should not be the subject of an immediate decision, the full implications of which cannot now be foreseen For this reason we are unable to accept the principles set out in the draft circular, but if you decide nevertheless to proceed with your proposals to create these new posts we think that their terms and conditions should be discussed with us either in the Working Party or by direct consultation between the Ministry and the Joint Committee We understand that the Working Party will be free subsequently to make what recommendations it thinks fit with regard to their future, subject to the provision of the same security of tenure for the holders We regard it as an important part of its subsequent task to see that this situation does not recur

As our discussions with you cover more points than are dealt with in this correspondence we assume that an agreed statement covering our discussions will be published together with these letters

Yours sincerely,
W RUSSELL BRAIN

18th April, 1958

Dear Sir Russell,

Thank you for your letter of 16th April I was glad to note that the Joint Consultants Committee welcome my proposal of the joint working party with the Ministry to study, in the light of the experience of the hospital service since 1948 and of all other relevant considerations, the principles on which the medical staffing structure in the hospital service should be organised The working party would of course cover the whole staffing structure and in the case of Senior Hospital Medical Officers I see no objection to its dealing with the points which Committee " B " of the Medical Whitley Council have recently decided to investigate, always providing that there is no objection from Committee " B " itself Of course I do not envisage that the working party will deal with pay

I can understand that holding the views they do the Committee would prefer to leave over the problem of special posts for time-expired senior registrars until the working party has completed its report But, as I have said, my proposal is purely an interim one and although we all hope that the working party will be able to complete their task within a year, the problems are complicated and I am sure that neither of us would want consideration of the very difficult questions that will arise to be hindered by pressure to produce a speedy report because of the immediate problems of individual time-expired senior registrars Nor do I think that these individuals should have to wait on the working party for some further assistance with their present position

I enclose a draft of the statement I propose to make in reply to a question which has been put down for answer on the 21st I hope you will not find that this will raise difficulty on your side

Subject to the last paragraph of the statement, I shall be very glad for the terms and conditions of the new posts to be further discussed between the Ministry and the Joint Committee, but for the above reasons we really must come to a speedy decision

I shall of course see no objection to this correspondence being published if you wish

Yours sincerely,
DEREK WALKER-SMITH

⁂ The statement by the Minister in the House of Commons on April 21 is reproduced on p 906 —ED L

Public Health

THE HEIGHTS AND WEIGHTS OF EDUCATIONALLY SUBNORMAL CHILDREN

A PARRY JONES
M B Wales, D P H
DEPUTY MEDICAL OFFICER OF HEALTH, CHELTENHAM, GLOS

W MURRAY
HEADMASTER, THIRLESTAINE COURT E.S N SCHOOL, CHELTENHAM

THE 1944 Education Act has helped to revolutionise the approach to the education of the handicapped child The main type of handicap is mental backwardness, and, since 1945, 153 special schools for educationally subnormal (E S N) children have been opened in England and Wales,[1] more being planned for the immediate future

Admission to these schools is generally on the grounds of mental backwardness—i e , poor scholastic attainment combined with a low intelligence quotient (50–75) But we noticed that often the children were also backward *physically*, though there was seldom any disease to account for their physical retardation This apparent difference was such that we decided on a detailed investigation, and accordingly we measured the heights, weights, and intelligence quotients of the children attending two junior E.S N day schools in neighbouring towns

In presenting our findings we have used the height and weight indices of Sutcliffe and Canham[2] These indices numerically resemble intelligence quotients (the normal being 100), and we have used them so that our measurements can be readily compared with those of normal children.

Sutcliffe and Canham compiled their figures from the heights and weights of seventeen thousand boys and girls in various parts of England, including our own. These tables have a possible disadvantage in that they were compiled in 1948, and we wondered whether they might be out of date So we took the average heights and weights of the children seen at school medical inspections during the last year and converted them into Sutcliffe and Canham indices The readings varied from the normal of 100 up to 103 Hence we regard these indices as satisfactory for the purposes of this investigation

TABLE I—HEIGHTS OF E.S N CHILDREN (BOYS AND GIRLS COMBINED)

Age (yr)	Height index								Total
	Below 70	70	80	90	100	110	120	130 or more	
7	—	—	1	1	—	—	—	—	2
8	1	2	5	1	1	3	1	—	14
9	1	3	6	7	5	1	—	—	23
10	2	4	3	7	5	3	1	—	25
11	3	3	8	5	2	1	1	1	24
12	3	1	5	9	9	1	—	—	28
13	1	1	3	—	3	1	1	—	10
Total	11	14	31	30	25	10	4	1	126

Tables I and II show that 73% of the children attending these E S N schools had weight indices below the normal of 100, and that 68% were also below the average in height. Whereas with normal children the majority of heights and weights fall within 90–110 on this index scale, with these E S N children the majority fell within 80–100 both in height and weight. Among the remainder, more children were at the lower end of the scale than at the higher Thus we are in no doubt that there is a considerable difference in physique between normal children and those in our two E S N schools

We did not detect any significant difference between the measurements of the boys and those of the girls The degree of underdevelopment was spread evenly between all age-groups except the youngest, in which the number of children examined was small

We do not claim that these observations are original More than twenty years ago Burt found that the dull and the intrinsically backward suffered primarily from retarded (physical) development[3] In 1941 Boas[4] wrote of American children

TABLE II—WEIGHTS OF E.S N CHILDREN (BOYS AND GIRLS COMBINED)

Age (yr)	Weight index								Total
	Below 70	70	80	90	100	110	120	130 or more	
7	—	—	—	1	1	—	—	—	2
8	1	1	4	2	—	4	—	2	14
9	—	2	5	9	4	1	2	—	23
10	3	3	7	5	4	3	—	—	25
11	2	2	9	7	1	—	1	2	24
12	2	3	5	9	6	1	1	1	28
13	2	3	4	1	—	—	—	—	10
Total	10	14	34	34	16	9	4	5	126

> "A study of the data collected shows an unexpectedly high relation between intelligence quotients and stature. Children short for their age had an I Q markedly under the norm, those tall for their age, one above the norm "

Recently the standard of living in this country has risen, but in our E S N schools the findings are much the same as those of Burt twenty years earlier This might suggest that the relation between physical and mental retardation is independent of environment, but we think that the more likely explanation is that these recent social improvements are not in fact reaching all children Certainly many of the E.S N children under our care have not benefited as fully as might be expected In some homes laziness and thoughtless spending of money may lead to an unnecessary lowering of standards which adversely affects the children

We do not wish to imply that a poor home environment is necessarily a major cause of the poor physique of E S N children This is a problem that has not yet been disentangled Burt[3] wonders how far this physical and mental difference between the bright and the dull

> "is due to the direct effect of a healthy life and diet upon the manifestations of intelligence, as judged by the ordinary tests, how far it is due to the fact that the more intelligent families are both able and willing to give better attention to hygienic conditions, and how far it is an outcome of a fundamental impulse to grow more rapidly in all directions "

An answer might be forthcoming if direct additional feeding could be provided for these underdeveloped children With the expansion of the special-school programme as a result of the 1944 Education Act, more and more E.S N children are being segregated The experiment of direct additional feeding would now be administratively easier, and the effects, if any, could be more readily measured In our opinion the provision of extra food and milk in E.S N schools would be well worth trying, and the results might be rewarding

The views expressed here are our own and are not necessarily those of the Cheltenham Committee for Education

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[1] Ministry of Education pamphlet no 30, p 3 H.M Stationery Office, 1956

[2] Sutcliffe A, Canham J W The Heights and Weights of Boys and Girls London, 1950

[3] Burt, C. The Backward Child London, 1946

[4] Boas, F *Science*, 1941, 93, 339

Poliomyelitis Vaccine

In written replies on Monday to questions about the supply of poliomyelitis vaccine, the Minister of Health said that about $6^1/_2$ million doses of vaccine were needed for the programme of vaccinating pregnant women and children under 15, towards this, 2 million doses were in the hands of local authorities by the end of February Orders had been placed with two British firms and (for 5000 litres of Salk vaccine) with one United States and one Canadian firm For different reasons there was a hold-up in supply in each of the four sources When the first difficulties arose in the supply of British vaccine, a further 2800 litres of Salk vaccine had been ordered, as well as further supplies when the Salk vaccine due last week did not appear Some British vaccine was now being distributed, and, barring further unforeseen difficulties, much larger supplies (mainly of Salk vaccine) would be ready next month Further supplies of Salk vaccine were being ordered The Indian Government had imposed certain restrictions on the export of monkeys, but these had not so far interfered with the manufacture or testing of vaccine in this country

A batch of vaccine (250,000 doses) from the Wellcome Foundation was held up by sickness of the test monkeys, this batch has now been passed and distribution has begun According to press reports, the Canadian source, Connaught Laboratories, believe that there has been a "misunderstanding in London" the contract was for 4 million doses before the end of June, and half of this had been supplied, the director knew that the British authorities wanted extra supplies in March, but the domestic demand had been exceptionally heavy just then The United States source, the Pitman-Moore Company of Indianapolis, said that 1,300,000 doses destined for Britain were held up because 1 virus out of 50,000,000 in a testing sample was found to be alive

A batch has arrived in London for testing of the consignment of 1,500,000 doses ordered as an emergency from the Parke Davis Company of Detroit A large proportion of this is said to be in stock and to have passed the tests of the company and the United States authorities The British tests normally take about $2^1/_2$ months

Case of Smallpox in the Wirral

A boy, aged 2 years, who lives about 400 yards from New Ferry Smallpox Hospital (where a seaman is lying ill with smallpox [1]), and who had not been vaccinated, fell ill on April 6 A rash appeared on April 9 and by April 14 was profuse all over the trunk, arms, and legs, and confluent on the face, the palms and soles were affected Asian smallpox was confirmed Since an attack of mumps he had not been out till about March 22, and then in a wheel chair There were few contacts outside the home All contacts have been vaccinated and are under surveillance, his relations living at home are remaining indoors, and their shopping is being done by a health visitor The child was admitted to New Ferry Hospital, and on April 20 was reported to be much better

New Recommendations in Industrial Diseases

The Industrial Diseases Advisory Council was asked to review all the diseases prescribed under the Industrial Injuries Acts (except pneumoconiosis and byssinosis), and its subcommittee has now issued a report,[2] with recommendations, which have been accepted by the Minister of Pensions and National Insurance

The Council suggest an inquiry into elbow conditions in trades involving manual labour They recommend that the description of poisonings by certain substances (e g , lead, benzene) should be extended to certain of their compounds, and that there should be changes in the definitions of industrial dermatitis and radiation injuries Slight changes were recommended in the wording concerning the cover provided for tuberculosis

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[1] See *Lancet*, March 29, 1958 p 686

[2] Ministry of Pensions and National Insurance Review of the Prescribed Diseases Schedule Cmnd 416 Obtainable from H M Stationery Office 1s *9d*

Parliament

Opticians Bill

At the report stage of this Bill [1] an amendment was accepted adding a fourth ophthalmic specialist to the General Optical Council, thus raising the number of medical representatives from 5 to 6

In moving the third reading of the Bill Mr **Richard Thompson**, parliamentary secretary to the Ministry of Health, said that it left the House in better shape than when it was introduced The promoters had accepted modifications to meet the views of the House The Bill now provided that the register of ophthalmic opticians should be in two parts, those proposing to test sight only and those proposing to test sight and to dispense glasses Amendments had also been accepted which prohibited the testing of sight except by a registered medical practitioner or a registered ophthalmic optician, and the sale of optical appliances except by or under the supervision of a doctor or optician An amendment had been added defining the scope of the optician's work in relation to the work of the medical practitioner Mr Thompson was glad that it had been found possible to introduce wording into the Bill which defined these responsibilities satisfactorily It was important that the optician should not overstep the boundary between his functions and those of the doctor He looked forward to a constructive partnership between opticians and doctors in the future as a result of the Bill and of the setting up of the General Optical Council

QUESTION TIME

Senior Registrars

Mr **Kenneth Robinson** asked the Minister of Health if he would now make his promised statement on the senior registrar problem —Mr **Derek Walker-Smith** replied The Joint Consultants Committee and I have agreed to set up a joint working party to study, in the light of experience of the hospital service since 1948 and of all other relevant considerations, the principles on which the medical staffing structure in the hospital service should be organised

I have concluded that—pending and without prejudice to the working party's report—the current arrangements for senior registrar posts should be modified in certain respects, in view of the fact that some senior registrars have long completed the normal tenure of their posts but have not yet succeeded in obtaining a higher post I am satisfied that these senior registrars should be given an opportunity of remaining in the hospital service whilst they continue to compete for higher posts, and hospital boards are being asked where necessary to offer extended contracts pending the working party's report

Also without prejudice to the working party's report, I am asking hospital boards to submit proposals for designating a limited number of senior registrar posts—mainly from among those already existing—which will provide responsible work commensurate with that which is normally expected of a fourth year senior registrar, will carry a higher rate of pay, will offer security of tenure, and will be available to senior registrars who have completed the normal period of appointment in the grade The senior registrars selected for these posts will of course be free to continue to compete for higher appointments I will emphasise to boards that these senior registrar posts are not to be regarded as a substitute for additional consultant posts

The Secretary of State for Scotland is discussing with the Scottish Joint Consultants Committee the application of these arrangements to Scotland

Mr **Robinson** Is the Minister aware that the interim arrangements which he has announced may be a satisfactory solution to the short-term problem, but that the only tolerable solution to the long-term problem is a considerable expansion of consultant posts? Why is it necessary to set up a working party to come to that very obvious conclusion? Mr Walker-Smith We have to look at the number of consultant posts which are desirable in the light of the staffing structure, and also of the economic context I hope that we shall get a quick and valuable report from this working party, and I prefer to wait for that

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[1] See *Lancet*, 1957, ii, 1166 & 1234

Sir Keith Joseph Will the Minister note that it is not commonly accepted that the only long-term solution is an expansion of the consultant force, since the economics of the service to the public and the location of the consultants in relation to the public demand that those factors must be examined most carefully? Mr Walker-Smith I will certainly bear in mind those valuable and constructive suggestions

Dr Edith Summerskill All that the Minister has said today is that the matter is to be postponed once more, and that the anxiety of these senior registrars is to continue for an indefinite period Is he aware that these men are being offered excellent opportunities in the United States of America, and that if there is to be another postponement we shall lose some of the best doctors in the country?—Mr Walker-Smith From the right hon. Lady's purported precis of my answer, I am afraid that either she did not hear or did not understand what I said If she will be good enough to read it, she will find that there is a great deal more for the senior registrars than she has said

Merit Awards Committee

Mr Robinson asked the Minister what was the size of the committee on merit awards to consultants of which Lord Moran was the chairman, and how many of its members were psychiatrists —Mr Walker-Smith replied 14, besides the chairman and the lay vice-chairman. None is a psychiatrist. Mr Robinson Without necessarily drawing the conclusion that the abysmally low number of merit awards to psychiatrists is connected with their non-representation on the committee, does not the Minister agree that this important specialty should be represented on the committee? If the Royal College of Physicians is unwilling to nominate a psychiatrist, will the Minister instruct the committee to seek nominations from the Royal Medico-Psychological Association?—Mr Walker-Smith In this matter I follow the recommendations of the Spens report, that the members of the awards committee should be appointed from nominations made by the Royal Colleges, the Scottish Royal Corporations, the Medical Research Council, and the universities The nominations of those bodies are in personal capacities and not representative of specialties

Russian Vaccine for Multiple Sclerosis

Mr Somerville Hastings asked the Minister if he had any further statement to make regarding the Russian vaccine for multiple sclerosis, notably its toxicity —Mr Walker-Smith Not yet, but inquiries are being pursued Mr Hastings Is the Minister aware that a certain amount of recent research has been carried out in Belfast, which associates this vaccine with rabies and that this has given rise to a very great deal of anxiety in the minds of the public?—Mr Walker-Smith It has recently been established that the vaccine is made from the brains of rats or mice infected with the rabies virus No further evidence is available as to the safety of the vaccine in treatment, but research is going on.

Dr Summerskill As a question of this kind was put to the Minister very many weeks ago and he assured us then that he was looking into the matter, why has it taken him such a long time? He must recognise that during this time many patients suffering from disseminated sclerosis have been waiting hopefully for some statement from him.—Mr Walker-Smith I have not been inactive in that matter I was asked to look into the New Zealand question, which I have done No evidence of the efficacy of the vaccine is available from there I am seeking information from the Russians through the appropriate channels Therefore, my position is at present that I can agree to the release of small private imports of this vaccine, but the patients' doctors in those cases have to agree to accept responsibility for the treatment.

Regional Distribution of Consultants

The numbers of consultants and other medical staff (including whole-time, part-time, and honorary staff) in hospitals under the regional hospital boards at the end of 1956 were given in whole-time equivalents in a written answer on April 15 and are shown in the second and third columns of the following table The estimated number of staffed beds and population in each region, given in the fourth and fifth columns, are taken from an earlier answer[1]

Regional hospital board	Consultants	Other medical staff*	Number of staffed beds (excluding beds allocated to mental illness and mental deficiency)	Estimated population (in thousands)
Newcastle	332	352	15,338	2944
Leeds	232	334	17,753	3066
Sheffield	285	456	19 716	4230
East Anglian	121	136	7254	1485
N W Metropolitan	420	641	17,930	3942
N E Metropolitan	317	502	18,966	3103
S.E Metropolitan	355	439	19,933	3229
S W Metropolitan	505	770	25,216	4707
Oxford	134	178	7433	1503
South Western	259	330	16,621	2792
Welsh	234	365	15 494	2608
Birmingham	400	421	23,047	4547
Manchester	323	593	23,611	4381
Liverpool	196	353	14,180	2130

* Excluding house-officers and general practitioners

Medicine and the Law

Doctor Charged with Manslaughter

At an inquest at Bridgend, Glamorgan, a coroner's jury returned a verdict of manslaughter on the ground of reckless negligence by a doctor[2]

In evidence, the doctor said that a woman of 39 consulted him on Dec 2, "six days before she had a miscarriage", but that he saw her next day (Dec 3) and "then discovered that she had had something done to her" The doctor thought that she was on the verge of pneumonia, and not that she had septicæmia She was under his sole care from Dec 8 to Dec. 23, he called in no other doctor She died in hospital from septicæmia At the first consultation she had asked the doctor to end her pregnancy, and he had refused

After the inquest the doctor was formally charged and granted bail

Death of a Boxer

A verdict of death by misadventure was recorded, at a Manchester inquest on April 17, on a boxer who died after lying in semicoma for 321 days following a contest.

The boxer, aged 23, was said to have collapsed in the dressing-room soon after the bout, in the last round of which he was sent down with two blows to the chin He had been warned that, because of a head injury sustained in a contest in the Army, he should never box again, but he went on with his boxing career

Two operations had been attempted on the man's brain At necropsy, there was no fracture of the skull, and the surface of the brain showed no evidence of laceration The meninges were thickened and stained yellow, indicating previous hæmorrhage, there was no trace of a blood-clot Death had been due to bronchopneumonia following internal hydrocephalus caused by traumatic subdural and subarachnoid hæmorrhages A pathologist said that the condition could have been caused by a blow on the jaw, this was comparatively rare, but "quite a number" of cases had been reported

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[1] See *Lancet* April 5 1958, p 748

[2] *Times*, April 19, *Manchester Guardian*, April 19

In England Now

A Running Commentary by Peripatetic Correspondents

"AND there," said the Salesman, turning a handle round and round, "after one minute you have all the vegetables cleaned and peeled and ready for cooking No messy peelings to deal with, every scrap goes down the sink, and what's more, for storage you just slap it against any wall and the suction feet keep it there " Suitably impressed, we returned home a few bob lighter, clutching our shining new 'Veg-O-Lux' I suppose the fault was really in us and ours rather than in the machine When the Architect, in powdered wig and knee-breeches, supervised the erection of our house he didn't bargain for a veg-o-lux

The Salesman couldn't understand why the sink had got blocked up, but he sold us a handy little chap called the 'Basin-Unstoppa' guaranteed to recanalise the most recalcitrant thrombosis Much encouraged, we returned to the leguminous battle and all went well until the time came for disposal we slapped it gaily on the kitchen wall and the sucker feet brought four tiles straight off This time the Salesman got rid of a tin of 'Tile-U-Up' When the thing brought down a shelf, he sold us some 'Neva-Slip' brackets

The whole episode to me had a familiar pharmaceutical ring Drugs tend to procreate themselves in just the same way Get a good new tablet and before the end of the year there are four or five others in use to counter its side-effects Either that, or it procreates a long line of modifications, side-chain derivatives, analogues, and so on Then the bubble bursts and you are back to square one It happened with liver extracts and it's happening now with tranquillisers (and not before time) All Life moves in cycles if not indeed in circles, though perhaps we like to think ourselves a little further on each time I suppose we usually are It remains to be seen whether this vegetabular circle has helped much after all, it seems that vacuum cleaners are being superseded by the revolutionary new carpet sweepers that require no electricity and do not harm the pile, my wife, too, finds more and more clothes that she prefers to wash by hand instead of subjecting them to the eviscerations of the washing machine At this rate by 1960 we shall be cooking our meals over an open fire in the back garden yes—and may be that's not so funny

* * *

Since the publication of the paper by Douthwaite on Pitfalls in Medicine,[1] I have been considering writing a companion paper on Medicine in Pitfalls

The telephone rings at 4 30 A M "Would I come at once —three men buried " I pull on my old gardening clothes and set off for the pit The Manager is waiting and tells me that one man got clear and two are buried I put on pit boots and helmet and we set off for the shaft through the crowd of men at the shift change The van from the mines rescue station with emergency surgical equipment arrives, the driver tooting rather importantly as he drives through the crowd We get our lamps, arrange for a haulage lad to carry the equipment, and then drop down half a mile Underground, an official meets us with the latest news One man is almost clear, they have located the other and he seems to be alive We set off for the coal-face and quite near it meet the stretcher party with the first man He appears to be in reasonable shape with a possible fractured ankle I ask the first-aid man to treat it as a fracture and send him out We dump our main equipment and start to crawl down the face with a small emergency bag The face height is about 3 ft 6 in, but the effective height is reduced because it has been prepared for "filling" and is obstructed by much newly blown down coal

The fall begins about 30 yd along the face The Manager leads, and when we get near he says "There seems to be some groaning and moaning, have a look at him " I find myself in a space about 3 ft wide with a nasty dark void above and the fall in front The man is trapped now only up to his knees and two men are digging away cautiously to free him There is no room for anyone else By the time I have given some morphine he is free We drag him under a good roof and find that although tired and weak he seems to have no gross injuries A stretcher is pushed up and the waiting helpers carry him along the face This is an awkward task because of the restricted height and rough floor His main complaint is that the pieces of string he used to keep up his socks are cutting into his swollen legs This is easily put right and he is covered up ready for the journey to the pit bottom

At this stage a grinning toothless veteran speaks to him "How are ye, Jim?" he says "They didn't make all this b—— fuss when I were buried "

* * *

My score for doctors on the Aldermaston march was higher than that recorded by my peripatetic colleague last week I counted eight—a physician, a surgeon, a pædiatrician, a virologist, a Colonial medical officer, and three G PS The last group included me, the only one to go all the way—in my car which was bespattered with red crosses *My patients* (what a pity I don't practise in London, Middlesex, Bucks, and Berks, they could all have been temporaries) were many—some with exhaustion, a couple of faintings, a dozen sprained ankles, two chickenpoxes, and over three hundred pairs of blistered feet

* * *

Nowadays one rarely has the opportunity to describe a new clinical syndrome, and only my inherent modesty prevents me from calling mine by my own name (Also the fact that I am reserving my name for my Nobel prize-winning effort) Alternatively I could name the syndrome after the first person to manifest the new disease But one of the patients was born in Poland and his name is unpronouncable, and to call it Addison's disease after my second patient would only lead to confusion So rather reluctantly I have been forced to adopt the old dermatological device of using a descriptive name, and the name I have finally selected is "Subacute phenindione pigmentary palmosis" There are two varieties var sinistra, and var dextra, the latter being the more common form

Curiously enough, though phenindione (var 'Dindevan') has been in clinical use for some years I have only lately seen my first 2 cases of S P P P Both patients complained of a patchy orange yellow discoloration of the right palm It did not itch nor was it found anywhere else Both patients had tried to wash it off without success and both were much perturbed by the phenomenon One had even travelled five miles to hospital especially to consult me about it They were both familiar with the orange-yellow pigmentation which is seen in (alkaline) urine and which could be confused with the colour produced by blood But neither of them had spotted that their disease arose from their habit of holding the pills in their right hand before swallowing them By passive transfer tests—i.e , holding the bottle in the other hand—I was easily able to transfer the disease to the opposite palm This was a much more elegant method of demonstrating its origin than by holding the tablet itself and brought home the point that it was advisable to empty the pills into a spoon

Several points remain to be elucidated Why has the syndrome not been spotted for so many years—after all we have been using phenindione for quite a while Is it only dindevan that does it? What of 'Hedulin' and 'Indema', which as far as I know are different trade names for the same substance? Is it associated with the alkaline tide of meals and only found in those who take their pills some time *after* a meal, or can it occur in those taking their pills while in a fasting state? All these points are at present under intensive investigation* and I hope one day to publish a further report on this new and fascinating syndrome Confirmatory reports are awaited with interest

* * *

Yesterday I received through the mail a small long-playing record from an American pharmaceutical firm One side recorded a one-year clinical study of the firm's newest preparation; the other the Vienna State Opera Orchestra playing Brahms' *Hungarian Dances* The drug advertised is a tranquilliser

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[1] Douthwaite A H *Brit med J* 1956, ii, 895

* Supported (in part) by Research Funds UR MAD 43 and IM DIM 999

Letters to the Editor

ADMINISTRATIVE THERAPY

Sir,—You are to be congratulated on your foresight in accepting, and giving pride of place in last week's issue to, Dr Clark's excellent paper

The subject is in its infancy and the paper gives a clear account of matters upon which the future success or failure of the psychiatric hospitals and perhaps the general hospitals of this country may depend

These matters have until now been bedevilled by national and local politics, the Ministry need for control through biddable men, the wild individualism of hospital medical staffs, and the now notorious and non-merited epitaph of so many medical superintendents "Administration does not count"

It is hoped that Dr Clark's paper will arouse interest in the subject at a date early enough to prevent the present generation of administrative therapists, administrative psychiatrists, medical superintendents, or whatever name they go by, being the last of their kind, for unless sufficient interest is aroused the treatment of the patient as a member of a group, which in the hospital he is, will be disregarded, psychiatry, covering nearly 50% of all hospital beds, will become the appendage of business management, and it is for the consideration of general hospital medical staffs that already they have travelled far along this road

Prudhoe and Monkton Hospital,
Prudhoe-on-Tyne

George McCoull
President, Medical
Superintendents Society

Sir,—Dr Clark, in his second last paragraph, says " the most important task of the administrative therapist is to establish the atmosphere of the hospital He needs openness, consistency, respect for everyone's human dignity, and a welcome for everyone's contribution "

This is very true I think it is a pity, however, that this is the nearest that Dr Clark gets to facing the fact that senior medical staff, by which I mean consultants and S H M O s, must take part in the administration of the mental hospital and must share with the superintendent in the making of policy decisions if the hospital is to work at its maximum efficiency This fact seems to me to be recognised in the Ministry's recommendation that medical advisory committees, consisting of senior medical staff, should advise hospital management committees and regional hospital boards Surely this implies that senior medical staff share with the medical superintendent ultimate responsibility for every aspect of hospital functioning They certainly cannot discharge this responsibility unless they share in the making of policy decisions

The tendency of consultants to indulge in " the flight into treatment ", which Dr Clark describes, may very well be a manifestation of the " apathy and withdrawal " described by Schwartz as occurring in groups deprived of the responsibility attaching to their position

I also regret that Dr Clark appears to believe that "As he [a medical administrator] treats his staff so will they treat the patients " This statement is self-evidently untrue But perhaps Dr Clark is merely saying again what he has said earlier in his article—that disturbed relationships between senior medical staff result in disturbed relationships between nursing staff and patients

Shenley Hospital, near St Albans

D Bardon

THE FUTURE OF THE PUBLIC HEALTH LABORATORY SERVICE

Sir,—The answer to A Provincial Pathologist (April 12) is that despite the millions of pounds spent annually, and largely wasted, on antibiotics, and the serious problem of hospital infection, bacteriology is not recognised as a specialty in the National Health Service in England and Wales The only bacteriologists connected with the hospital service are the select band employed by the universities in the medical schools If a bacteriologist wishes to obtain a post in the National Health Service he has to do so in the guise of a general pathologist or an assistant pathologist and work under the direction of a consultant pathologist-in-charge who is either a morbid anatomist and cares nothing for bacteriology, or a clinical pathologist who thinks he knows it all (as well as hæmatology, clinical biochemistry, surgical histology, and forensic pathology)

If A Provincial Pathologist studies the literature he will know that nearly all the significant contributions to medical bacteriology in the past ten years have been made by workers outside the National Health Service If he studies the advertised vacancies he will see that the only advertisements for hospital bacteriologists come from Scotland, where there is a more enlightened view of the importance of bacteriology in the diagnosis and treatment of infective disease and the control of hospital infection

A London Bacteriologist

TOXÆMIA OF PREGNANCY

Sir,—Professor Theobald (April 12), by casting algebraic pebbles into the ripples of the toxæmic clinical pattern, cannot obscure the design whose periphery on occasion develops into the eclamptic wave, despite the prophylactic antenatal oil applied to the surface of the pool to still its waters

His classification of the toxæmic state correctly interpreted reflects the normally mounting severity of the underlying renal changes responsible for the production of, at first, the œdema (a result of the reduction of the glomerular filtration), next, the hypertension (a result of cortical renal ischæmia), and, finally, the albuminuria (a result of the slowing down of the renal circulation) In fact his data, unwittingly, further support the renal intervention, by demonstrating that a severe degree of renal ischæmia if prolonged leaves its stigma on the kidney in close resemblance to the experimental effect of sufficiently prolonged clamping of the renal artery in animals, in whom irreversible renal changes are thereby produced His data also offers proof of the uterorenal reflex, for by denervation of the uterus and interruption, thereby, of the uterorenal pathway he has succeeded in preventing toxæmia—an achievement for which he deserves the highest credit, if I may be permitted so to judge

Conjecture of disharmonious function of various hormones in the ætiology of toxæmia has no validity in fact or by inference from available data Such disharmony cannot be advanced to explain postpartum hypertension and proteinuria, which already find satisfactory explanation on the basis of the uterorenal reflex[1] Although Professor Theobald admits the intrusion of an inadequate blood-supply to the placenta as being of ætiological significance, he completely fails to appreciate the influence of the resistance to stretch of the uterine muscle in provoking it and thereby overlooks the stimulus responsible for the uterorenal reflex that by imposing renal ischæmia causes the toxæmic manifestations

The impact of geography and diet are those of superimposed effects on the ætiology, acting either for good or for ill They can be so assessed inasmuch as they help to influence the size and the chemical constitution of the body compartments, which in their turn benefit or impede the renal function disturbed by the pre-eclamptic process

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[1] Sophian, J *Lancet*, Feb 22, 1958, p 434

London, W 1 JOHN SOPHIAN

SALT IN PREGNANCY

SIR,—Dr Robinson (Jan 25) undoubtedly showed great moral courage, for she must have realised from the first that she would cause among obstetricians feelings of shock, surprise, and even disbelief, when stating that she treated 20 patients with toxæmia of pregnancy, with good result, by allowing them extra salt

It is this part of her investigation that interests me most Personally I regret that Dr Robinson did not measure the aldosterone output during periods of salt-free diet and compare it with the output during periods when extra salt was given

According to prevailing opinion, when extra salt is given the production and urinary output of aldosterone diminish, the same may be true of the quantities of aldosterone stored in the adrenal cortex, so that when this and other hormones are suddenly liberated from the adrenals (e g, by histamine produced by an antigen-antibody reaction) smaller quantities of hormones are available and ultimately reach the circulation, which circumstance must have a favourable influence on the course of toxæmia

However, Dr Robinson's results are so unexpected that I quite agree with Dr Thomas (April 12, p 793) that it is of the utmost importance to verify or challenge these results, because they may very well modify our therapeutic concept of toxæmia of pregnancy

Amsterdam R SCHUURMANS

ONE RADIOGRAPH TO EXCLUDE PLACENTA PRÆVIA

SIR,—Dr Earn and his colleagues in your issue of April 19 have done well to draw attention to the efficacy of soft-tissue placentography in excluding placenta prævia One wonders though if they have not oversimplified the picture

Given ideal conditions one tilted standing lateral view of the uterus and pelvic brim is enough to diagnose placenta prævia or exclude it where the radiographic signs are definite But not infrequently conditions are not ideal and then the signs may be indefinite Intestinal stasis and an abundance of gas that accompany rest in bed will often interfere with accurate interpretation Around 34 weeks too the smallness of the fœtal head may allow the existence of a minor though significant degree of placenta prævia without much displacement Even slight hydramnios may be enough at this stage to make diagnosis indefinite

But what your contributors have failed to stress is the great need for the fœtus to be lying axially with one or other pole centrally over the brim at the time of the X-ray It is the responsibility of the obstetrician to see to this and to be present at the radiographic examination for this purpose—otherwise a useless and misleading film may be taken and the patient and fœtus needlessly exposed

When we published[1] the results of 275 placentograms in your journal in 1955 we stated that the error should be nil if the diagnosis "border-line placenta prævia" in doubtful cases is used We made 3 errors in diagnosing 50 placenta prævias—none serious In our next 275 placentograms there were 40 placenta prævias with 1 diagnostic error due to a thin membranaceous placenta prævia Thus in 550 placentograms for diagnosing 90 placenta prævias the error was less than 1%, the combined fœtal mortality (corrected) for placenta prævia was 8 8% and there was no maternal death The 17% error of your contributors for placenta prævia we feel is much too high and is in danger of detracting from the merits of an accurate technique

We think that soft-tissue placentography is a very reliable method so long as proper regard is given to its basic principles One radiograph certainly should be the aim though not always achieved (it has been ours for some time past), and for this reason all possible care should be given to both choice of the patient and suitability of the fœtal lie

The London Hospital, E 1

ROBERT PERCIVAL
STANLEY MURRAY

SIR,—I cannot entirely agree with Dr Earn and his colleagues that a single lateral radiograph of the uterus is sufficient to exclude placenta prævia Admittedly they would be correct in the vast majority of cases, but there is one fallacy which they appear to have overlooked I have now had more than ten years' experience of this method, and on several occasions I have found normal appearances in the lateral radiograph with evidence of placenta prævia—sometimes of a major degree—only in the anteroposterior view taken in the semi-erect position

Harrogate FRANK REID

SUPPORT FOR THE FAMILY

SIR,—In your leading article of April 5, you stated that as a result of my survey of old age in Bethnal Green, I had put forward the suggestion of a constant attendance allowance to be offered to relatives who undertake the care of bedridden old people In fact I suggested that the allowance might be payable not to relatives but to bedridden pensioners themselves, this was only one of a number of recommendations put rather summarily at the end of a book devoted to the family life of people of pensionable age

I found that the strongest and most enduring relationships between adults in a family were those between people who gave a great deal to each other, every day as well as in emergencies If her daughter had a paid job a grandmother often prepared meals and looked after one or more of the grandchildren (whether or not they lived with her) while the married daughter, for her part, did the shopping and heavy cleaning Old people were invariably less happy when they could no longer "do their share" and contribute materially to a relationship It seems there may be three or four bedridden old people at home for every one in hospital or residential home Too often a relative bears the strains of nursing with little support, while the old person has no opportunity of useful occupation or of making the relationship of dependence less one-sided This is why I argued that an allowance should be paid to the old person rather than to the relative He or she may then be in a better position to pay independently for any special needs and to repay the relative for the care given Of course, many practical questions relating to a "personal attendance allowance" would remain unanswered in thus settling a matter of principle by appeal to the findings of one sociological investigation

Department of Social Science,
London School of Economics and
Political Science London, W C 1

PETER TOWNSEND

*** We refer again to Mr Townsend's valuable survey in an annotation on p 895 —ED L

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[1] Lancet, 1955, i, 1045

EPIDEMIOLOGICAL INQUIRIES

SIR,—Working in the field of health education, we are very dependent on the findings of epidemiology, but being accustomed to think that the knowledge and attitudes of the people concerned may be a vital factor in the epidemiology, we are often disappointed that it is not generally taken into account

I am at present engaged in working out an epidemiological inquiry card which, in addition to the usual information about personal and environmental factors, is intended to include questions regarding recognition of the condition by the population at risk, knowledge about the condition, attitudes towards it, and finally behaviour regarding it

As I am sure other workers have considered this point, and as I am particularly aware of the difficulty of validating such questions, I should be glad if you would give me space to ask any who are interested or who have trodden this path, to communicate with me

Central Council for Health Education,
Tavistock House North,
Tavistock Square,
London, W C 1

JOHN BURTON
Medical director

THE DOCTOR'S ATTITUDE TO HIS PATIENT

SIR,—Although it is hardly possible to have the Rev John Wesley read Scanner's letter (April 12) ("The emotional history should not have any direct influence on the doctor's clinical opinion the clinician reaches that opinion without the emotional history, and can give just as good advice and can get just as good a result without ever hearing it"), we must hope that Scanner's patients will insist that he reads the Journal of the Rev John Wesley "Whence came this woman's pain (which she would never have told had she never been questioned about it)? Why, then, do not all physicians consider how far bodily disorders are caused or influenced by the mind?" (*Lancet*, April 12, p 763)

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CORONARY-ARTERY DISEASE

SIR,—In your editorial (March 22) Horlick and Craig[1] are quoted as showing that "in some subjects such an action [specific cholesterol-lowering effect] was seen on giving ethyl linoleate and linoleic acid in pure form"

While it is true that when ethyl linoleate was substituted for the mixed fats of the normal diet, the serum-cholesterol fell, we also noted that when ethyl linoleate was given to an individual on a low-fat diet whose cholesterol levels had stabilised, there was no further fall in cholesterol We concluded that ethyl linoleate possessed no specific cholesterol-lowering effect and that effects observed with it were due to the removal of animal fats from the diet when isocaloric diets containing linoleate were prepared Our results differ from those of Kinsell et al[2] who reported that linoleate lowered the blood-cholesterol of subjects on a low-fat diet

Careful perusal of their data (2 cases) shows that in case 1 (27-year-old male with familial hypercholesterolæmia) the serum-cholesterol fell from a level of 326 on the low-fat diet to a level of 291 at the end of seven days on 80 g of ethyl linoleate daily In their second case (19-year-old male with fractured femur) the cholesterol fell from 145 at the end of two weeks on a fat-free diet to 95 after one week on 80 g of linoleate per day

Considering the rather wide fluctuations in day-to-day cholesterol levels seen in both of these subjects the results can only be considered significant in the second subject It should be noted that whereas our subjects were healthy and mobile, carrying on their regular work as medical students, Dr Kinsell's subject was immobilised with a healing fracture It is conceivable that such differences may influence the results obtained

Because of the scanty data available, I believe that it would be premature to draw any conclusions concerning the role of essential fatty acids in cholesterol metabolism and atherogenesis

University Hospital,
University of Saskatchewan,
Saskatoon

L HORLICK

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[1] Horlick L Craig B M. *Lancet* 1957 ii 566

[2] Kinsell, L W, Michaels G D, Friskey, R A, Splitter, S *ibid* Feb 15, 1958, p 334

LONG-TERM ANTICOAGULANT THERAPY FOR CORONARY-ARTERY DISEASE

SIR,—Your leading article (Feb 22) gives the impression that a novel simplified technique has been devised by Manchester[1] to solve the problem of venepuncture for the multiple prothrombin tests required This impression is quite erroneous (and Manchester[2] himself does not subscribe to this notion), since similar techniques were suggested by Quick[3] and Kato[4] for assessing prothrombin deficiency in infants We[5] adopted the better components of these procedures and, using a modification of a method[6] for freeze-drying thromboplastin, elaborated a simplified technique using capillary whole blood In effect, all the operator has to do is to reconstitute the dried brain extract with water and mix 0 02 ml of it with an equal volume of capillary blood and note the clotting-time We claimed no originality for the test, but recommended its use by the practitioner, when laboratory facilities for the usual one-stage prothrombin method during anticoagulant therapy were not available.

Our students are instructed in the capillary technique, because many will become practitioners in the country away from laboratory facilities The method became so popular that, when long-term anticoagulant therapy was instituted in Dr Suzman's unit at the Johannesburg General Hospital, it was used in controlling therapy in outpatients Today over 50 estimations are done at the weekly follow-up prothrombin index (P I) clinic, and the first detailed analysis of the results was published by my colleagues[7] who, together with others, speak highly of the method This report deals with 82 cases treated continuously with anticoagulants for periods up to seventy-six months

Although the simplified technique has been known for a long time it is surprising that it has not been applied more generally When our paper was abstracted by Brown,[8] he rightly criticised us for not having provided more statistical analysis than the bare coefficient of correlation of 0 82 between the capillary method and the usual laboratory method However, he misinterpreted our caution in applying the method for general use in anticoagulant therapy as an indication that the technique was inaccurate We were concerned that the method might be used for the "prothrombin response to vitamin K" test in the differentiation of intrahepatic and extrahepatic jaundice,[9] and so bring this diagnostic test into disrepute However, the deviation between the capillary and intravenous methods can be considerably reduced by practice and is no longer a hindrance to the acceptance of the procedure for the control of anticoagulant therapy

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[1] Manchester, B *Ann intern Med* 1957, 47, 1202

[2] Manchester, B, Rabkin, B *Circulation*, 1954, 10, 691

[3] Quick, A J *Proc Soc exp Biol*, N Y 1939, 42, 788

[4] Kato, K *Amer J clin Path* 1940 10, 147

[5] Stein H B, Wallace, B V *S Afr med J* 1952, 26, 353

[6] Souter, A W, Kark, R *Amer J med Sci* 1940, 200, 603

[7] Suzman, M M., Ruskin, H D, Goldberg, B *Circulation*, 1955, 12, 338

[8] Brown, A *Abstr World Med* 1952, 12 297

[9] Stein, H B *S Afr J med Sci* 1942, 7, 72, *ibid* 1944, 9, 111

In their authoritative book on blood-coagulation, Biggs and Macfarlane[10] also dismiss microtechniques as not being sufficiently reliable Our own tendency to exercise caution in recommending the capillary method is due to the fact that no laboratory worker will voluntarily substitute it for the usual Quick[11] technique, I myself[12] have written disparagingly of "bed-side" procedures for estimating prothrombin, since it is impossible to perform multiple tests on the same sample or to control the temperature and other conditions of the test However, mass-production demands simplified methods of control, and the experience of the local outpatient P I clinic shows that the method is one in which skill is soon acquired by attentive medical registrars and house-physicians

At one end of the scale of one-stage prothrombin methods there are simplified capillary techniques, and at the other the relatively complicated "prothrombin and proconvertin" method of Owren and Aas[13] All the methods require care and attention to technical details, of which the most important is the concentration and standardisation[14] of the only significant reagent used in the test—namely, tissue (brain) thromboplastin

Department of Pathology and Microbiology,
Witwatersrand University Medical School,
Johannesburg, South Africa

H B STEIN

TRANSTHORACIC LIGATURE OF ŒSOPHAGEAL VARICES

SIR,—In my book, Portal Hypertension, I appended the name of George Crile, Jr, to the operation of transthoracic ligature of œsophageal varices because I believe that he was the first to describe it adequately It has never been my intention to give the impression that Dr Crile himself had written the chapter, as suggested by the review in your issue of April 12 The chapter was written by me and the methods are strictly my own, following what I understand to be those of Dr Crile I sincerely hope that Dr Crile will forgive me for any misunderstanding that may have arisen

London, W 1

ALAN H HUNT

*** We ask Dr Crile's forgiveness for our part in this misunderstanding —ED L

THE HARVARD STEP TEST

SIR,—There appears to be some disagreement among experts as to how this test should be conducted

In *The Physiology of Muscular Exercise* by Schneider and Karpovich and in *Circuit Training* by Morgan and Adamson, it is stated that pulse readings should be taken 1–1½ mins, 2–2½ mins, and 4–4½ mins after 5 minutes of step-ups Other books by Larsen, McCloy, Clarke, and Reidman quote the time for pulse readings as 1–1½ mins, 2–2½ mins, and 3–3½ mins It appears therefore that there are two separate tests In an endeavour to find which, in fact, is the Harvard step test I wrote to the American Association for Health, Physical Education and Recreation They have confirmed that Dr Lucien Brouha, of Harvard University, advocates the second method quoted above, and sent me a reprint, from the *Research Quarterly*, of an address delivered at Springfield College entitled The Step Test—A Simple Method of Measuring Physical Fitness for Muscular Work in Young Men This is dated December, 1942

It does not seem to matter much which test is used as both are an effective way of measuring cardiovascular fitness What does, however, matter is to know, when comparisons are being made between the physical-fitness indices of well-known athletes, that the results quoted have been computed in the same manner if a fair comparison is to be made I believe that the Amateur Athletic Association's coaches have been testing athletes in this country and using the first method of testing and not the recognised method of conducting the Harvard step test

An authoritative statement on the correct method of conducting this test and computing the physical-fitness index would be most welcome and a great help to physical educationists and athletic coaches

Physical Education Department,
St Luke's College, Exeter

W R CAMPBELL

RADIATION, LEUKÆMIA, AND MALIGNANT DISEASE

SIR,—An important point has been lost sight of in the strenuous correspondence concerning the communication by Dr Alice Stewart and her colleagues,[1] regarding the relationship of radiation, leukæmia, and malignant disease the paper was a *preliminary* communication Dr Stewart, one imagines, was so concerned at the possible importance of their initial findings that this publication was submitted at once, surely it is equally admirable that the Editor of *The Lancet* commented upon it in an editorial[2] A preliminary communication means what it says, and as one of those who has been most generously and courteously allowed to see some of the data, may I endorse the pleas of you and Dr Stewart to wait and see After such attacks it can be understood that the final report will be being very carefully prepared

I could not help raising my eyebrows at Dr Jackson's accusation (March 29) that Mr Hewitt has "merely found what he sought" I am afraid that perhaps Dr Jackson does not wish to find what he may see

Child Development Unit,
University of Louisville School of Medicine
Department of Pediatrics
Louisville, Kentucky

FRANK FALKNER

TREATMENT OF OBESITY

SIR,—Dr Mullins' letter of April 5 on the perennial problem of the overweight rightly points out the dangers of obesity and the advantages of reducing to normal limits In theory the majority of overweight patients reducing intake by a diet lose weight In practice for a variety of reasons it is not so easy for the individual to stick to a diet Help is needed, but I am surprised to find she considers strict supervision is essential, as this is contrary to my experience on the whole

For a number of years I have been employing weight reduction methods using only hydrophilic colloids These are given ½ to 1 hour before normal mealtimes in the form of liquid preparations which "deceive" the stomach and produce an effective anorexia (One of these methods suitable for hospital use is described elsewhere[3]) In the few cases of apparent failure or partial failure almost all such patients admitted that they had not followed instructions, had been casual about them, or had decided they no longer wished to reduce Only in such cases does strict supervision become imperative

I note that Dr Mullins uses various drugs, some of them very potent, in her supervised regime However, in many cases reducing can and ought to be carried out in the patient's home, and if this is to be done without strict supervision certain essential conditions must be observed The criteria which seem important to me when considering a "weight-off" method are (1) complete freedom from danger, non-toxicity, and complete absence of side-effects (thus, in my opinion, rules out the use of potent “ drugs ”), (2) efficiency of action, (3) simplicity of use, (4) low cost, (5) that the rationale should be capable of convincing translation into a simple story which the patient can appreciate—this I consider most necessary in gaining the patient’s full cooperation Certain of the hydrophilic colloid group fulfil these criteria admirably and are capable of preparation at low cost in hospital pharmacies However weight reduction methods are “ modish ” creatures In 1912 there were at least 24 proprietory “ treatments ” [4] all of which have fallen by the wayside Today a dozen or so methods come to mind including 3 or 4 potent drugs, and in the future we shall no doubt meet new variations of method

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[10] Biggs R, Macfarlane R G *Human Blood Coagulation and its Disorders*, p 334 Oxford, 1957
[11] Quick A J, Stanley Brown M, Bancroft, F W *Amer J med Sci* 1935, 190 501
[12] Stein H B *S Afr J med Sci* 1941 6 93
[13] Owren P A, Aas K *Scand J clin Lab Invest* 1951 3 201
[14] Stein H B, Abrahams O L *S Afr J med Sci* 1954, 19, 75, 79, 91

[1] Stewart A, Webb J, Giles, D, Hewitt D *Lancet*, 1956, ii, 447
[2] *ibid* p 449
[3] Badham J N *ibid*, 1953, ii, 1316

St Albans J N BADHAM

USE AND TOXICITY OF SULPHONAMIDES

SIR,—It is good that Dr Arneil (April 19) has sounded what I hope will be the death knell of that dangerous drug, sulphamerazine

It is good, too, that in your annotation you emphasise the value and safety of sulphadimidine Alas though, too many doctors only know of this drug as ‘ Sulphamezathine ’ which, to the ear, sounds little different from sulphamerazine I have often found it necessary, when recommending the use of sulphadimidine, to add the proprietary name by way of explanation

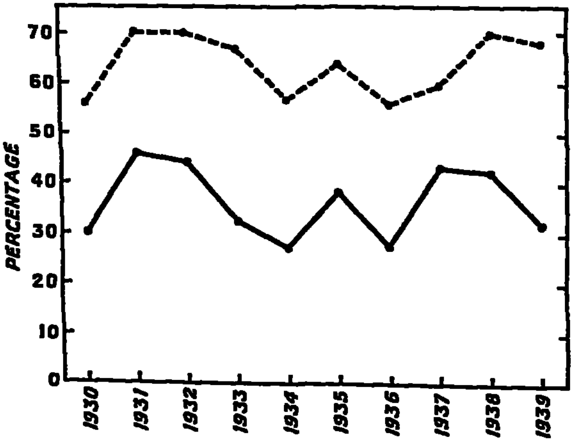
Cannot the manufacturers suggest a way of avoiding this confusion? Greater prominence of the official *B.P* name on their labels would help

Derby BERNARD M LAURANCE

TREATMENT OF BREAST CANCER

SIR,—Mr. Bond and Dr Waterhouse (Feb 22) and Dr George Crile, Jr (April 5) are correct in implying that “ the strong challenge from the Mayo Clinic ” is indeed no challenge at all, except perhaps to those folk who seem unable to assess the proper significance of published figures Your editorial certainly presents the Mayo Clinic figures in somewhat tendentious fashion, and though you find it difficult to compare “ figures from the Mayo Clinic and those from Edinburgh ” one is glad to see that your correspondents do not experience the same difficulty

The close correlation between survival-rate and the stage of the disease is well brought out in the accompanying figure from a series of 1044 cases seen at St Bartholomew’s Hospital [5] The figure shows the crude five-year survival-rate for patients with breast cancer registered between 1930 and 1939 inclusive Also shown is the percentage of cases placed in clinical stages I and II each year The graph of survival-rate is closely paralleled by that of the clinical staging, and this figure is analogous to that shown in Mr Bond and Dr Waterhouse’s letter



1044 cases of breast cancer Continuous line—5-year-survival rate in all cases registered Broken line—percentage of cases in clinical stages I and II

The age-distribution of the patients is also relevant in the comparison of different series, yet you make no mention of this point Even in the absence of this information about the Mayo Clinic series, it would seem that the figures do no more than support the maxim that the apparently good results are mainly, if not wholly, the results of selection

Radlett, Herts REGINALD S MURLEY

NEW METHOD OF PHENOBARBITONE ADMINISTRATION

SIR,—Although my experience here is limited to one “ hystero-epileptic ” patient, and a period of four weeks, Dr Pearson’s (April 19, p 853) critical comments on Dr O’Connor’s innovation (March 22, p 609) prompt me to say that this patient (who over the last two years proved impervious to any form of therapy) has changed beyond recognition since being put on phenobarbitone ‘ Spansules ’

Wyke House Hospital,
Isleworth, Middlesex H PULLAR-STRECKER

FLEXION SPASMS AND CONTRACTURES IN SPINAL-CORD DISEASE

SIR,—My interest in the paper by Mr Platt, Dr Ritchie Russell, and Dr Willison (April 12) prompts me to make the following comments on some of their statements

It is indeed gratifying that clinicians are becoming more and more aware of the various intrinsic and extrinsic factors that influence spasticity in patients suffering from spinal-cord afflictions, and, in this connection, the beneficial effect of utilising postural reflexes in the counteraction of flexor spasms, as postulated by previous workers, is confirmed by the authors

On the other hand, their sweeping statement that, in cases of spinal-cord disease causing severe paraplegia, a day or two in bed may lead to permanent loss of all capacity to be other than chair-ridden or even bed-fast is, to say the least, exaggerated, if not altogether misleading Furthermore, I was surprised to read the authors’ criticism of anterior rhizotomy of lumbar and sacral roots for relieving spasticity by claiming that it produces such wasting of gluteal muscles that sitting becomes uncomfortable This view will hardly be acceptable to neurosurgeons who have had experience with this method, nor is it in accordance with the vast experience gained on patients with conus/cauda-equina lesions or residual paralysis following poliomyelitis If anterior rhizotomy is contemplated in patients where severe and intractable spasms and contractures of the hip flexors and adductors are predominant, complete atrophy of the gluteal muscles can be avoided by sparing L4 or L5 roots

Judging from the immediate postoperative condition of their third case, following their technique of combined bilateral obturator resection and iliopsoas resection in one session, it is obvious that their procedure is no less formidable and hazardous to the patient than anterior rhizotomy, and anyone contemplating this type of operation would be well advised to carry it out in stages

The authors, in the techniques of physical therapy described, have very closely followed the principles and details of treatment introduced and practised during the last 14 years in the National Spinal Injuries Centre, Stoke Mandeville, and have freely used its resources In their description of their first case, whom I had the opportunity to see myself in consultation, I missed any reference to the remarkable beneficial effects of hydrotherapy in our swimming-pool—not only as an overall training effect but, indeed, in this particular case, as a most efficient method of relieving spasticity Moreover, this patient is photographed in a walking-chair which I designed a few years ago specifically for exercises for paraplegics with complete or incomplete lesions I assume that the authors did not realise that this design had not been published (it will be described in detail elsewhere), as they would otherwise no doubt have made due reference

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[4] More Secret Remedies British Medical Association, London, 1912

[5] Williams, I G, Murley, R S, Curwen, M P *Brit med J* 1953, ii, 787

National Spinal Injuries Centre,
Stoke Mandeville Hospital,
Aylesbury, Bucks

LUDWIG GUTTMANN

*** This letter has been shown to Mr Platt and his colleagues, who write "We are sorry that Dr Guttman is so critical of our methods of treating flexion spasms and contractures Our approach to the problem differs in several respects from those which he has developed so successfully for cases of traumatic paraplegia, but we think he will find that the method now described proves to have some important advantages We were unaware that the walking-chair used to support the patient for the photograph had any special features"—ED L

SIR GEORGE SAVAGE AND THE SANDS OF TIME

SIR,—I saw a good deal of Sir George Savage (1842-1921), as my father was virtually an old Guy's man and a personal friend of Addison, who presented him with a copy of his bust that used to stand in the hall of his house in Grosvenor Street

Savage contributed many interesting articles, written for the students, to the *Guy's Hospital Gazette*, which I eagerly read, as my father continued to be a subscriber to the *Gazette* until his death One of the articles that fascinated me was entitled The Sands of Time, and I think it ought not to be forgotten It described some of the mental troubles of old people, and fancifully compared the mind of an old person to the sands on a desert, blown about by the wind A storm would blow away the top layer of sand and expose an underlying layer, which might be taken to correspond to a fanciful memory of remorse for having once stolen a sixpenny piece as a boy A fresh storm might expose another layer, which unfortunately corresponded to the memory of having once told his father a falsehood At last fresh winds might arise and cause a new layer to be reached, which fortunately corresponded to one of the happiest memories of his life

London, N W 1

F PARKES WEBER

INFANTILE GASTROENTERITIS

SIR,—The answers to many of Dr Librach's questions (April 5) relating to fundamental work on infantile intestinal flora are to be found in various articles [1–5] as well as textbooks of pædiatrics and bacteriology

Dr Librach is no doubt aware that many commensals (including *Escherichia coli*) are pathogenic outside their normal habitat, and that some are potentially so in their own systems—e g, pneumococci and staphylococci in the respiratory tract In this example there is a further similarity to *Esch coli* gastroenteritis in so far as certain types (or strains) of these organisms are involved more than others in the production of pneumonia

In all infections the host plays an important role In the case of gastroenteritis, favourable living conditions in the small bowel for *Esch coli* are provided by the diet of cow's milk (the carbohydrate protein ratio amongst other factors) With regard to transmission, the agents in intestinal infections (including viruses) enter the bowel usually by mouth, at which they may arrive in many ways, and there seems to be no reason to doubt that infection with *Esch coli* is acquired in the same way as with shigellæ and salmonellæ

It seems to me that the interpretation of the presence in fæces of an "enteric" virus, which may be as widely distributed as *Esch coli*, would present almost the same problems as exist with the serotypes of *Esch coli* in question, which have been associated consistently with the disease (if I may call it so) at least since the 1920s [6] Finally, for a comprehensive account of the ætiology I would refer Dr Librach to the Royal College of Physicians of Edinburgh Publication no 5 [7]

City Hospital, Greenbank Drive,
Edinburgh, 10

G SANGSTER

POSTOPERATIVE HYPOTENSION

SIR,—As you say (March 15), postoperative hypotension is relatively common, and it is seen particularly in patients returned to the horizontal from the lithotomy position

In 176 cases of major vaginal surgery, a significant degree of hypotension was found in 101 (57%) [8] Of a series of 75 cases of anæsthesia for perurethral prostatectomy, which I hope to publish later, in 36 (48%) the systolic pressure fell to below 100 mm Hg, or to a level more than 50 mm Hg below the preoperative level, when the legs were lowered

As you also say, routine recording of the blood-pressure after operations is not common practice Quite a number of the above patients had none of the recognised signs of hypotension Indeed, they had an easily palpable pulse at a rate within normal limits they were dry, warm, and of good colour, and they were conscious and cooperative

The dangers that beset these patients may be illustrated by two cases

Both patients, on return to the ward, appeared so well to the nurse that they were propped up to encourage drinking Both quickly became unconscious, had a further fall in blood-pressure, and soon showed signs of shock Fortunately, laying the patients flat and applying restorative measures resulted in obvious improvement

Until recovery-rooms with trained staff are as standard in the theatre equipment as operating-tables and anæsthetic machines, such incidents are certain to recur Meanwhile it is of vital importance that postoperative hypotension should be recognised and that doctors and nurses should be aware of its inherent dangers

Glasgow

WOOLFRED SNIPER

PILONIDAL SINUS OF THE UMBILICUS

SIR,—With reference to the article by Dr Sadeghi-Nejad and Mr Rains (March 15), it may be of interest to report a similar case

A hirsute Italian man aged 34 came to see me recently complaining of a sore navel Examination revealed a similar picture to the illustration shown, a bundle of downward pointing hairs with roots orientated inwards, protruding from the umbilicus, in which there was some moist intertrigo The umbilicus was held open with forceps and the bundle was withdrawn Most of the hairs were free, but the root ends of a few were embedded in a small mass of granulation tissue lying at the bottom of the pit The granulations were touched with silver nitrate and the soreness subsequently subsided

I referred him to Mr Gordon Bohn who found a few more loose hairs at the bottom of the umbilicus and agreed that no further treatment seemed necessary

Sonning Common nr Reading

P M R HEMPHILL

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1 Dawson W C *Amer J Dis Child* 1925 18 743
2 Gerstley J R Howell K M Nagel B R *ibid* 1932, 43 555
3 Hall I C O'Toole E *ibid* 1935, 49 390
4 Blacklock J W S Guthrie, K J Macpherson I *J Path Bact* 1937, 44, 721
5 Crowley H Downie H W, Fulton, F Wilson, G S *Lancet*, 1911, i, 590
6 Adam, A *Jb Kinderheilk* 1927 116 8
7 Smith J Royal College of Physicians of Edinburgh Publication, no 5 1955 see *Lancet* 1955 ii 1182
8 *Canad Anæsth Soc J* 1956, 3, 216

Obituary

DANIEL ALEXANDER DAVIES

B Sc Wales, F R C S

COMBINING general practice with surgery in a way which has now become difficult, Alec Davies, of Walmer, was a man who brought warmth and vigour into all he did His strong surgical leaning found expression in his work at the Victoria Hospital, Deal, but he was essentially a good all-round doctor, whose therapeutic ability came largely of liking people and taking much trouble to help them

Entering St Thomas's Hospital in 1920 with a B SC from Wales, he qualified in 1922 and later became resident-anæsthetist at the hospital Soon after taking his F R C S in 1926 he settled in Deal, where he quickly built up a reputation by his high standards of practice Over the years he came to number among his patients several eminent colleagues, and their confidence in him was a tribute to his medical skill and his honesty of purpose

In the 1914-18 war he had served in the Welsh Guards (in which he always retained great pride and interest), and in the second war, though aching to serve abroad, he managed to relieve his feelings by combatant training of the local Home Guard Though there was, in the end, no invasion, there was also war surgery to be done in Deal The bombing and shelling of the early days and the damage done to his home perturbed him not at all, but merely increased the trenchancy of his remarks about the enemy and all their works

Soon after the war Davies had the first, and almost fatal, attack of coronary thrombosis which he described so vividly in our Disabilities series His method of managing it was the then unusual one of ignoring symptoms and returning at the earliest possible moment to full work Nor did he confine his interests and activity to his practice The St John Ambulance Corps, the Royal Cinque Ports and Sandwich Golf Clubs, the Betteshanger Rugby Football Club all enjoyed his constant support He kept up a close attachment with St Thomas's Hospital and had lately been elected a representative of St Thomas's on the United Hospitals Club He also found time to serve on the Kent and Canterbury executive council and on the South East Kent hospital management committee

The following tributes show something of his quality as a man and his skill as a doctor H L writes

Alec Davies was an able man, practical and gifted with a large fund of common sense, a clever diagnostician, and a general-practitioner surgeon of the first rank Kindness and sympathy he gave readily to anyone who was in real distress, but he spent little time on malingerers, he hated humbug and any action he thought not straight He was progressive and kept his knowledge up to date not only by the study of journals and modern textbooks, but by frequent visits to his old hospital where he attended the wards, operating-theatres, and occasional lectures One could not fail to be impressed by the way in which he tenaciously clung to what was good in the clinical teaching of the days when he was a student and on the house During his visits to St Thomas's he enjoyed meeting students, asking them questions, ragging them, and giving them tips that would be useful to them when they were in practice On looking back, one feels that if he had had the opportunity he would have been a very sound and popular teacher

J S H, who worked with him for many years, describes him as a general-practitioner specialist who was "as much at home as a family doctor in a miner's house as in the operating-theatre of his local hospital"

We shall always remember Alec Davies (he continues) for his disarming forthrightness of speech, irrespective of the company in which he found himself His comments on any trying situation were invariably direct and colourful, but a gift of humour in his forceful expressions robbed them of offence, as indeed did the friendly charm and interest he bestowed on all who knew him One could always rely on him for an amusing story, carefully graded to the company in which he found himself, yet in his private life he was of a serious disposition, and technical reading, especially of articles on modern surgery, was perhaps his main occupation at home He was a careful diagnostician, and many resident medical officers at the local hospital will have been edified by his practice in waving away X-ray films and reports until his thorough clinical examination of a surgical case had been concluded Both Deal and the hospital service will miss the help of an experienced practitioner who combined the skills of general practice with the outlook of a highly qualified consultant surgeon

Another friend recalls Alec Davies' talents as a writer and a reader

He had the ability to make written words come alive, as though he were talking He had wit and eloquence which, if disciplined, could have made him a notable writer, as he was a notable person Once or twice—his language a little tempered—he published his current opinions on the National Health Service, and for some months he had been incubating what he called his second Bevan lecture on the subject Though never one of those controversialists who go out of their way to do justice to the other side, he could always be relied on to say something wise, as well as something enjoyably wild His pleasure in writing went with a love of books, and he was an ardent reader both of general and professional literature

He died in Deal Hospital on April 8, at the age of 60, and leaves two daughters

WILLIAM HALLIBURTON McMULLEN

O B E, M B Lond, F R C S

Mr McMullen, consulting ophthalmic surgeon to Charing Cross Hospital, London, died on April 15 at the age of 81

His father was a doctor in Camberwell, and he was educated at the City of London School and King's College He qualified from King's College Hospital in 1898, and after holding house-appointments at King's he took the F R C S in 1901 After holding the posts of curator and pathologist at the Royal Westminster Ophthalmic Hospital (now part of Charing Cross Hospital) he was appointed assistant surgeon to that hospital Later he also joined the staffs of the Miller General Hospital, The Hospital for Sick Children, Great Ormond Street, and the Royal Northern Hospital During the 1914–18 war he was ophthalmic specialist to the Central London recruiting depot After he retired from his hospital appointments he remained a helpful and valued member of the house committee of the Royal Westminster Ophthalmic Hospital

He married in 1906 Miss Kate Higgins who survives him with three sons

M L H, who was one of Mr McMullen's clinical clerks, writes

Even in 1912 he was white-haired and of distinguished appearance He was a good teacher and extremely thorough in his approach to every case, even in a busy clinic This opinion I was able to confirm when I followed him as ophthalmic surgeon at the Miller Hospital, and saw many of his old notes and cases When, in 1934, I once again followed him, this time at Charing Cross Hospital, I was able to see how much his opinion on medical cases had been respected It was largely through his inspiration and planning that we were able, in 1930, to open our present hospital in High Holborn, with its 100 beds in place of the 40 beds of the old hospital Besides being a careful diagnostician he was a good and meticulous operator and very light-handed Even in illness he preserved the calm and unruffled exterior which was so characteristic of him

A memorial service will be held at 11 A M on Wednesday, May 7, at St John's Wood Chapel, London, N W 8

PAUL OSWALD WOLFF

Dr Med, Dr Phil Berlin

BEFORE he left Germany in the '30s, Professor Wolff had won a national reputation as a pharmacologist, as a university teacher, and as a medical editor He used his years of exile to win an international reputation as an expert on the problems of drug addiction and as a sectional chief of the World Health Organisation

He was born in 1894 in Berlin, the son of Geheim Sanitatsrat Dr Alfred Wolff, and studied medicine in Göttingen, Freiburg, Greifswald, and Berlin His career was interrupted by the war, in which he served in the German army and was disabled by gas, and he did not qualify till 1919 After taking his doctorates in medicine and in philosophy he joined the department of pharmacology in the University of Berlin, and became a Privat Dozent In 1925 he joined the editorial staff of the *Deutsche Medizinische Wochenschrift* and in 1930 he became editor-in-chief During these years he was also an adviser on drugs and drug addiction to the German Ministries for home affairs and for health and he was for some years secretary to the German Arzneimittel Komission He took an important part in drafting the regulations for the use of opiates which were accepted at the meeting of German doctors held at Danzig in 1928 and which are still current practice in Germany today

In 1933 Wolff emigrated to Switzerland where he became a regular contributor to the *Schweizerische Medizinische Wochenschrift* He also wrote several reports on narcotics for the League of Nations He was well fitted for this work by his mastery of English, Spanish, and French In 1939 he was sent to the Argentine on a mission for the League of Nations and he remained there till 1948, continuing his work for the League and also acting as an adviser to the Argentine Government In 1949 he returned to Geneva on his appointment as chief of the Addiction-producing Drugs Section of the World Health Organisation After he retired in 1954 he continued to lecture and write on the control of narcotics and in 1956 he visited this country to speak at a meeting of the Society for the Study of Addiction (of which he was a vice-president) His paper on heroin from the international point of view was later published in our columns Last year he was made an honorary professor of the Free University of Berlin

A man of high intelligence, a scholar, and a collector of works of art, Wolff was also an engaging companion, of deprecating humour Latterly frail, he made little concession to physical disability He was, as a friend says, "a man who never gave up", and to the day of his death, in November of last year, he was busy on his study of synthetic narcotic drugs

Diary of the Week

APRIL 27 to MAY 3

Monday, 28th

WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY, St Mary's Hospital Medical School, W 2
5 P M Prof C L Oakley Sites of Production of Antibodies
MANCHESTER MEDICAL SOCIETY
9 P M (University of Manchester) General Practice Dr R W Burslem Some Obstetric Difficulties

Tuesday, 29th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W C 2
5 P M Dr H G H Richards Thrombosis (Erasmus Wilson demonstration)

Wednesday, 30th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P M Dr M Jaupitre Le Cinéma Endoscopique en Urologie, Technique, Indication, et Intérêt
INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Dr R W Riddell Laboratory Procedures for Mycotic Infections
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P.M Dr J G Scadding Results of Antibacterial Treatment in Pulmonary Tuberculosis
OXFORD UNIVERSITY
5 P M (Radcliffe Infirmary) Dr Paul Weiss Mechanism of Wound Healing (Litchfield lecture)

Thursday, May 1st

INSTITUTE OF LARYNGOLOGY AND OTOLOGY
5 30 P M (Royal College of Surgeons of England) Prof W D M Paton Pharmacology of Mucous Membrane
INSTITUTE OF PSYCHIATRY
5 P M (Maudsley Hospital, Denmark Hill S E 5) Prof Delisle Burns (Montreal) Physiology of Amnesia
ALFRED ADLER MEDICAL SOCIETY
8 P.M (1, Wimpole Street, W 1) Prof Alexander Kennedy Psychology of Training and Competitive Sport
NUFFIELD ORTHOPÆDIC CENTRE, Wingfield Morris Orthopædic Hospital, Oxford
8 30 P M Mr R G Taylor Use of Bone Grafts in Delayed and Non-union of Fractures
UNIVERSITY OF BIRMINGHAM
4 P.M Prof E C Amoroso Constitution of the Mammalian Placenta (First Ingleby lecture)
ROYAL MEDICO-PSYCHOLOGICAL ASSOCIATION
4 30 P M (Cheadle Royal Hospital near Manchester) Psychotherapy and Social Psychiatry Dr G C. Heller *Schisms in Psychotherapy*
UNIVERSITY OF DUBLIN
5 P M (Trinity College) Prof A Hagedoorn (Amsterdam), Gross and Minute Defects of the Germ Cells and Clinical Ophthalmology

Friday, 2nd

ROYAL SOCIETY OF MEDICINE 1 Wimpole Street W 1
10 30 A M *Otology* Dr R B Lumsden Mr Spencer Harrison Dr Lionel Naftalin Dr G MacDowall Conservative Treatment of Menière's Disease
2.30 P M *Laryngology* Mr K Greer Malcomson Vasomotor Activities of the Nasal Mucous Membrane Mr A J Moffett A Possible Relationship between the Sinuses and the Lymphoid Tissue of the Naso-pharynx
5 30 P M *Anæsthetics* Dr Raymond Wise Treatment of Barbiturate Poisoning (Registrar's prize essay)
ST MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W 2
5 P M Mr T B Fitzgerald Contraction Ring Dystocia
UNIVERSITY OF BIRMINGHAM
4 P M Professor Amoroso The Functional Role of the Placenta (Second of two Ingleby lectures)

Appointments

FRANCIS, H W S, M B Cantab, D P H M O in charge of immunisation, Birmingham
HORNER, J S, M B Birm school M O and assistant M O H, Leicester
JONES, KINGSLEY, L R C P I, D P M assistant psychiatrist, St Andrew's Mental Hospital Group, Thorpe
JOSEPH, SARAH N, M B Madras, D OBST school M O and assistant M O.H, Coventry
KNOX, JOHN, M B Glasg, M R C P consultant physician, North-eastern Regional geriatric service, Scotland
MCFIE, JOHN, M D Cantab psychologist, National Hospital for Nervous Diseases, Queen Square, London
MACKENZIE, MAVIS H, M B Lond school M O and assistant M O H, Leicester

The Hospital for Sick Children, Great Ormond Street, London

BROWN, K, M B Sydney, F R.C S house-surgeon to the orthopædic and plastic departments
KOBLENZER, P J, M B *Lond assistant medical registrar*
VANIER, THERESE M, M B Cantab house physician

South Western Regional Hospital Board:

HEWITT, MARK, M B Lond, M R C.P part time consultant venereologist, West Cornwall clinical area
HUDSON, JOAN I, M B Cantab, D P M assistant psychiatrist, *Horton* Road and Coney Hill Hospitals, Gloucester
SHEACH, JEAN M, M D Aberd, D M R D consultant radiologist, Exeter clinical area

West Riding of Yorkshire County Council

BRISTER, ISOBEL K E, M B Brist, D OBST assistant M O and school M O, Kirkburton, Denby *Dale, Colne Valley, Meltham, Holmfirth* and Saddleworth
CUSACK, NORA, M B, N U I, D C.H, D P H assistant M O and school M O, Castleford
FARRER, J A, M B Melb senior assistant M O and school M O, Rowland, Sedbergh, and Settle
STALKER, ROBERT, M B Aberd assistant M O and school M O, Spenborough and Mirfield

Colonial Appointments

BOOKLESS D W, M B Edin, D P H senior M O Fiji
BROWN J D M B Belf M O, Kenya
CARUANA SALVINO, M D B SC Malta, D T.M & H D P H senior M O.H, Sierra Leone
CRAWFORD WILLIAM M B Dubl D T M M O, Somaliland
EGWUATU S O, M B N U I senior M O Eastern Nigeria
FRASER SIR JAMES, M B Edin F R C S E surgeon Sarawak
GRAY, D K, M B *Lond* M O, Fiji
IKPEME P J L M S Nigeria senior M O, Eastern Nigeria
MOLLER, M S G M D senior M O, health education Tanganyika
SEIFER, R M B M O Uganda
SMITH, C J C, M B Edin, F R C S E surgeon Sarawak

Notes and News

MEDICAL RESEARCH COUNCIL

A GROUP for research on the chemical pathology of steroids is to be established in Sheffield, under the direction of Dr J. K. Norymberski. The group will study steroids in relation to disordered metabolism in disease in general, not only in rheumatoid arthritis. The board of governors of the United Sheffield Hospitals, which is associated with the Council in establishing this group, is to provide accommodation at the Jessop Hospital for Women and to meet a third of the running costs; the board has received grants, of £4000 each, from the British Empire Cancer Campaign and the Sheffield and District Convalescent and Hospital Services Council, to meet capital costs.

The Council's obstetric medicine research unit, under the direction of Prof. Dugald Baird, is moving into new accommodation—an additional storey on the antenatal wing of the Aberdeen Maternity Hospital. The building costs are to be met by a grant of £60,000 from the Scottish Hospitals Endowment Research Trust, and the equipment and nurses will be provided by the North Eastern Regional Hospital Board (Scotland). There will be eight beds, besides laboratories and offices for the social research section, which should make possible intimate collaboration between clinicians and research workers. The work of the unit began during the late war with studies of perinatal mortality, which showed the significance of maternal nutrition; later studies showed the importance of the mother's physique, health, and social background. More information is sought on the social background of normal pregnancy, and on the biochemical changes during pregnancy (particularly in the sex hormones) and their relation to physiological efficiency in pregnancy and labour.

MINISTER'S REPLY TO SELECT COMMITTEE ON ESTIMATES

IN their report on the running costs of hospitals, the select committee on estimates made some pointed criticisms of the Ministry of Health, which have drawn an equally sharp reply from the Minister.[1] The committee said that it was clear to them that "if full value is to be obtained for the large sums of public money that are spent every year, there must be more time and attention devoted to long-term planning", and they expressed depression at "the apparent lack of vigour with which some fundamental problems are being faced by the Ministry".

The Minister dissents from the suggestion of lack of vigour, and asserts the opposite. As evidence he cites matters specifically mentioned by the committee that have already been the subject of action. Thus the committee made recommendations about the appointment and assessment of salaries of hospital administrators; both these recommendations, says the Minister, have been made by Sir Noel Hall in a recent report, which is being considered. The committee recommend the fullest use of departmental costing; the Minister agrees, and has already informed hospital authorities of the importance he attaches to it. In the past, costing returns have been taken into account in deciding allocations for developments; in future the more accurate information from departmental costing will be used. The committee urge that medical students should be required to know about the financial structure of the health service and the cost of treatments. The Minister points out that the chief medical officer of the Ministry has at intervals provided information to medical schools about prescribing costs and asked them to include it in the curriculum; a committee is at present considering the factors in the cost of prescribing. There has been a considerable increase in joint contracting, which is recommended by the committee. The committee also called for an inquiry into the domiciliary consultative service, and for a relaxation of the definition of capital to finance small revenue-saving projects out of savings in running costs; the Minister will institute the inquiries and consider the redefinition.

TEN YEARS OF THE SLOUGH INDUSTRIAL HEALTH SERVICE

IN Slough many factories are concentrated in a small area, in and near the Trading Estate; thus it lends itself to the type of cooperative industrial health service that was set up there in 1947.[1] The latest annual report surveys the first ten years' running of the service.[2]

When the Slough Industrial Health Service began there were 52 member firms, with a total of 6324 employees; now there are 179 firms, with 17,748 employees. The care of all the 11,500 employees of member firms that have no medical department of their own costs about £2 a head yearly; half of this is accounted for by the casualty service, which treats over 500 patients a day, 98% of whom continue at work after treatment; only 0·8% of new patients attending the general clinics have to be referred to hospital. There are consultants (an orthopædic surgeon, a plastic surgeon in charge of the hand clinic, and a cardiologist), who hold regular clinics, besides several full-time doctors on the staff experienced in industrial medicine and dermatology. In addition to the central and two peripheral clinics, there is a mobile dressing-station which visits the more distant factories and prevents much loss of time. About 12% of the patients attending the general clinics have eye injuries.

The clinics are supported by X-ray, pathology, and physiotherapy departments, and there is a social-service worker. Patients who need intensive reablement are treated (as inpatients or outpatients) at Farnham Park centre, which also attracts patients from hospitals in London and elsewhere; its cost, previously shared by the Service and the Regional Hospital Board, is now borne entirely by the Board. Besides all its remedial work, the Service provides an occupational hygiene service, headed by a physician, an engineer, and a chemist, which is equipped with chemical and dust laboratories and a workshop. This service, controlled jointly with the London School of Hygiene and Tropical Medicine, advises on, and investigates, environmental conditions in the factories of member firms and occasionally others. Finally, many manufacturers require their workers to have initial or periodic examinations, and these, as well as annual examinations of senior executives of certain firms, are carried out by the staff of the Service.

RELEASE BINDINGS ON SKIS

THE ski accident prevention committee of the Ski Club of Great Britain has expressed concern at "the apathy and even antagonism" of some skiers towards the use of release bindings. The committee sought to investigate 180 ski-ing accidents on which claims were paid by one insurance company in 1956–57.

A questionary was sent to each of the 180 people concerned, of whom 148 replied. Of these 148, 59 had used some form of release binding. Of these 59, 27 sustained injuries unrelated to their release binding (e.g., collisions). Of the remaining 32, 15 admitted that their bindings had been improperly adjusted, in 10 further cases the release had operated and only a minor accident (e.g., sprain) resulted, and in only 2 of the other 7 cases were the skiers fully protected by both forward and rotational release bindings.

In no instance, says the committee, did the wearer of a release binding directly blame it in any way for the accident. The committee found that the proportion of skiers wearing release bindings rose steadily from 1·6% in first-season skiers to 54·5% in sixth-season skiers. "It is obvious that the more experienced skier realises the value of release bindings."

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[1] Fourth Special Report from the Select Committee on Estimates. Session 1957–58. H.M. Stationery Office, 1958. Pp. 7. 6d.

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[1] See *Lancet*, 1953, i, 1241.

[2] The Slough Industrial Health Service, Ltd. Tenth Annual Report, 1956–57. Issued from the Community Centre, Farnham Road, Slough, Bucks.

CLOSURE OF HOSPITALS

WITH the passage of time, developments in medicine and changes in local circumstances will probably lead to more readjustments in the hospital service if the community is to be served efficiently and economically, and the *Minister of Health* does not wish to discourage hospital boards from closing hospitals or changing their use where this may seem desirable He has, however, the responsibility of safeguarding as far as practicable the original objects of a hospital, and he has now sent a leaflet to hospital boards (H M [58]29) asking them to consult him before any change and describing the procedure to be followed

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University of Glasgow

On June 18 the honorary degree of LL D will be conferred on Dr J Cruickshank, formerly professor of bacteriology in the University of Aberdeen, Dr T F Fox, editor of *The Lancet*, Dr E Husfeldt, professor of clinical surgery, University of Copenhagen, and Sir Hans Krebs, professor of biochemistry, University of Oxford

Royal College of Surgeons of England

At a meeting of the council on April 17, with Sir James Paterson Ross, the president, in the chair, Mr T Keith Lyle was elected a member of the Court of Examiners Prof R B Kerr and Prof E J Wayne were appointed Sir Arthur Sims Commonwealth travelling professors

It was agreed to establish a Court of *Anæsthesia* in the College

The following were elected fellows of the college without examination as being medical practitioners of 20 years' standing

Prof R W Scarff, Air Vice-Marshal John Conrad Neely, Mr George Bell, Mr G H Thomas, Prof F C Wilkinson, Prof A E Galloway

The Jacksonian prize for 1957 was awarded to Mr B B Milstein The council selected the subject for the prize for 1959 non-specific granulomata of the alimentary tract Mr P C Williams and Dr F C Chesterman were appointed Imperial Cancer Research Fund lecturers for 1958

Diplomas of fellowship were granted to P M Marnie and M F Sturridge

The following diplomas were granted, jointly with the Royal College of Physicians

D L O—A D Soysa

D O—A P Barclay, B J Bowden, B D Coote, C C Ewing, T P Griffith, W M Higginbottom, Elizabeth D Jamie, R V Kotnis, C G McEwen, I A Mackie, N L L Margetson, I A Mir G A I Namsoo, Margaret C W Neilson, J B Parton, Than Pe C O Quarcoopome, Dev Raj T V Ranganathan, A P Sah L F Shanahan Froma Somerville, Peter Taylor D O Tonkin, Ursula Walters

D T M & H—A J Berman T K Bose, J K Chakravartı, D D E W de Alwis Ugo Fornari M C Gupta, Maswoodul Haque, H T Heah, M D Heyman, F N C Ho, M H Husaini, R T Jensen P V Krishnamurti Leif Langlo, G R L Lyons W R McKibben P D Marsden, R J Onyango I S Pillay, Nargis N J Rana, B N Roy Louis Saint-Arnaud M Y Siddiqui J P Soonawalla Subramaniam Thanikasalam M McC Wilson C M Wylie

D Phys Med—A M Bain, J D K Palmer

On Tuesday, May 6, at 5 P M at the college, Lincoln's Inn Fields, W C 2, Dr H Rocke Robertson, professor of surgery in the University of British Columbia, will give the Moynihan lecture, on observations on wound infection

Social Security Agreement between United Kingdom *and France*

A revised convention on social security between the United Kingdom and France will come into force on May 1

The convention consolidates and replaces the provisions of the existing agreements It covers benefits for sickness, maternity, industrial injury old age, widowhood, and death, it extends French old age allowances to United Kingdom nationals, and it ensures that medical benefits under the French insurance scheme available under the earlier arrangements only to the families of United Kingdom nationals insured under that scheme may now be extended to British retirement and industrial injury pensioners and to persons receiving long term sickness benefit

Australian National University

Dr F C Courtice has been appointed to the new chair of experimental pathology in the John Curtin School of Medical Research at Canberra

Royal Anthropological Institute of Great Britain and Ireland

On Thursday, May 15, at 5 30 P M at the Institute, 21, Bedford Square, London, W C 1, Dr Raymond Cabannes, director of laboratories, *Faculty of Medicine, Algiers, will* lecture on the distribution of abnormal hæmoglobins in Algeria, Hoggar, and High Volta

Problems of Old Age

Mr Derek Walker-Smith, the Minister of Health, when he addressed the Conference of the National Old People's Welfare Council in London on April 17, discussed the pattern and underlying principle of what services for the old should be He reiterated that the best place for old people was in their own homes, with help from the home services if need be, but he pointed out that, however successfully this principle was applied, the time must come when the struggle to maintain independence becomes too great a burden for many old people to sustain with any satisfaction to themselves "The problem then arises," he added, "of knowing when this point is reached, just when the emphasis should be switched from helping people to stay independent, to encouraging them to feel that they might now find greater comfort and peace of mind in sharing life in a community with others in whom the means for self-reliance is running down" There was need for further investigation of these problems, and for that reason he welcomed the further grant offered by the Nuffield Foundation for a detailed factual study of the reasons why people enter *homes for the old*

Surgeon Rear-Admiral W R S Panckridge, R N, has been appointed an *honorary* physician to the *Queen in succession to* Surgeon Rear-Admiral David Duncan

Prof R B Hunter has received a Purdue Frederick Medical Achievement Award The award was announced by the International Council for Health and Travel

On April 21 the Freedom of Wolverhampton was conferred on Dr J H Sheldon, who has been a citizen of the borough for 37 years and is now senior physician at the Royal Hospital, Wolverhampton

Dr W T M Gilbert has been appointed an official member of the executive council of St Helena

At a public meeting to be held by the London Marriage Guidance Council on Thursday, May 8, at 8 P M, at County Hall, Westminster Bridge, S E 1, Dr Alfred Torrie will speak on the place of marriage counselling in the work of the family doctor

The Association of Medical Records Officers will hold an educational conference and exhibition from May 14 to 17 at the Sun Pavilion, Harrogate The speakers will include Dr W P D Logan, Dr W G Daynes, Dr J L Cates, Mr A W Purdie, and Dr C A Holman Further particulars may be had from Mr A L J Turner, the secretary of the association, United Bristol Hospitals, Royal Infirmary, Bristol, 2

This year for the first time the German Academic Exchange Service is offering a number of grants to young doctors who wish to visit German university institutes and clinics The grants (125 DM a month) are tenable from Oct 1, 1958, for twelve months or less Further particulars may be had from the London branch of the service, 43, Parliament Street, S W 1

CORRIGENDA *A Chair of Pædiatric Surgery*—In last week's annotation (p 839) we asserted that the new chair at the Institute of Child Health in the University of London was the second of its sort A correspondent informs us that such chairs are not uncommon in the U S S R

Control of Treatment in Myxœdema by Electrocardiography—In our issue of Jan 18 there were two errors in doses in the article by Dr P C Gibson On p 129 the dose in case 2 after 10 days should be gr 4½, not gr 1½, and on p 130 the maintenance dose in case 10 should be gr 1½, not gr ½

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SOCIAL MEDICINE IN DEVELOPING COUNTRIES *

CICELY D WILLIAMS
B.A., D M Oxon, F R C.P, D T.M & H
FORMERLY ADVISER IN MATERNITY AND CHILD HEALTH, SOUTH EAST ASIA REGION, WORLD HEALTH ORGANISATION

(concluded from p 866)

Welfare and Health

SOCIAL medicine, as its name implies, does not function in a vacuum, and its exponents must consider other forms of social enterprise. During the last fifteen years experiments in social welfare and community development have been made in various forms in various countries There have been drives for literacy and mass education, sometimes based on what is known as "fundamental education" In many places clubs have been organised, both for men and for women, with the object of improving agriculture, diet, domestic and community living standards by encouragement of self-help Aid has been provided for the handicapped, the aged, and the neglected, for as old tribal structures break down there has to be some more sophisticated type of social security to take the place of traditional forms

Where these experiments have been organised in cooperation with the basic departments of law, health, education, and agriculture, and where they have promoted the teaching of home economics, they have helped medicosocial work But sometimes they have diverted attention from essentials to less essentials For instance, money has been spent on recreation halls when schools and clinics were lacking A campaign to build latrines has not taken into account the fact that their use and maintenance would need a change in habits which could only be achieved by gradual education In programmes of "health and welfare", the work of the medical department has not been expanded, and "welfare centres" have been launched though trained medical staff was insufficient

The indiscriminate use of the expression "child welfare" has sometimes hindered work in child health Thus "child welfare" centres, which were originally devised for countries where child-health services were already provided by hospitals and by doctors in general practice, are being set up in places where proper medical facilities do not exist It is rather as if the Good Samaritan had started by giving the victim money for his journey before picking him off the road and attending to his injuries

It might be thought that in countries where there is a high infant and child mortality almost any work for children is better than none But schemes for welfare have sometimes deferred the establishment of organised health centres and hospitals, and recruited staff which was even more urgently needed by the health services

Medicine has a long, arduous, and expensive training Nursing is traditionally overworked and underpaid. But "social work" is regarded as a less exacting profession, and it is often easier to recruit large numbers of social workers than one or two nurses The social services sometimes offer not only an easier training and better salaries, but also better working conditions and better transport facilities As a result there may be no pupils at an excellent training school for health nurses, while in the nearby "community development" training centre large numbers are preparing for "health and welfare"

In one place a new health and welfare project was started in an area where health was a major problem. It began by a complete house-to-house census Later a medical unit was set up; but, though it was well staffed and equipped, it was little used by the people It was then pointed out that the original census had been made not by the medical but by the social workers I believe that had the medical workers taken part in this initial stage of the work they would have made their contacts when the people were most receptive, and the centre would have got off to a better start. As it was the medical staff missed their opportunity, and, in the face of many and untouched health problems, there was relatively little that the "social workers" could do

Some countries where rapid changes are taking place have serious problems of neglected and delinquent children Their maternal and child health services are still rudimentary, doctors cannot give enough time to the clinics, and the hospital provision for sick children is inadequate The health visitors have too large areas to cover, and spend so much of their time in travelling, that they have little left for visiting or keeping in touch with non-cooperative parents The authorities in these countries are now being urged to spend more money on children's homes and children's officers If they could instead be induced to expand and improve their maternal and child health services, this not only would be more economical, but most of these social complications and disasters would be avoided and both physical and mental health would be improved

Where epidemics of preventable diseases monopolise the hospitals, doctors take steps to prevent these diseases Where hospitals are crowded with accidents, behaviour problems, gunshot and stab wounds, alcoholics, and the usual flotsam and jetsam of social tides and storms, the doctors' duty is not only to salvage but also to try to prevent Certainly social welfare and community development have a valuable part to play in health education, in adult education, and in organisation of voluntary work. They can do much to extend the social usefulness of the medical departments If doctors and nurses were better trained in the social functions of medicine, they would be able to cooperate more effectively in community development schemes

Strains of Adjustment

The sophisticated countries have their own peculiar health problems, such as cardiac emergencies, peptic ulcers, allergies, and dental caries These are all beginning to appear in the developing countries No less serious are the problems in mental health, including the angry adolescents of all ages, the suburban neurotics, and a variety of social misfits

In the primitive village, behaviour is remarkably standardised Health and survival may be uncertain, but discipline and a certain social security are assured Many sophisticated people lack the poise, reserve, and dignity conspicuous in some of the less sophisticated communities

As territories develop economic independence and achieve more responsibility for self-government, more posts become available for men and women with training and skills which are very different from those needed in the scattered farms or isolated villages of a previous era But education brings new stresses It may separate the child from his unlettered relatives He leaves a world of uniformity which does not demand decisions and where every experience is shared with the family and with the community, and enters a world which he cannot share with his fellows He is confronted with enlarged possibilities but with the embarrassment of choice Too often he develops what is now called "cross-cultural shock"

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* Abridged from the Milroy lectures for 1958, delivered before the Royal College of Physicians of London on Feb 4 and 6

The education demanded or offered conforms to the orthodox European standards, leading to university qualifications Much of it is alien to some of the developing countries and this, too, produces a sort of unreality Of late, efforts have been made to modify curricula so as to make them more applicable to local conditions, but this is not always easy Though mechanical and scientific facts are the same all over the world, they are still strange to the primitive village

The permissiveness of modern education imposes an added strain on pupils accustomed to a stricter discipline

These stresses of education often show themselves in restlessness There is a tendency to flit from job to job, not only in search of higher wages but in order to explore as many openings as possible Often there is difficulty in achieving any sort of self-criticism

But even those who are not exposed to the strains of education have to adjust themselves to an unfamiliar monetary system, to town life, to regular work, to altered food habits, to commercial pressures, and to the relaxation of traditional authority Inevitably new disciplines and responsibilities impose a considerable strain, and it is not uncommon to find disorderly behaviour among workers who have found a new freedom and a new wealth but have failed to accept new sanctions Students in schools and colleges, and men and women in responsible posts may likewise prove unable to bear these stresses Cases of hysteria, schizophrenia, and other disorders are not uncommon Some recover, but others cannot use their enlarged opportunities In some areas the Christian missions have done much to provide stability and standards of conduct in a changing world In many of the mission hospitals equipment may be of a poor standard, yet the social medicine and the educational services are excellent

The indices of health are not only rates of mortality and morbidity but also the incidence of violence, crime, alcoholism, delinquency, and inadequacy If the medical services in developing countries were more aware of their social functions, they would become more respected as instruments of social policy

Assessment of Needs

Vital Statistics

The advanced countries can turn to vital statistics and records from the hospitals and medical services for guidance on their policy But in many of the developing countries vital statistics do not exist or are quite inaccurate, while hospital and other records may be both unrepresentative and unreliable

Where major epidemic diseases are prevalent, it is obvious, without waiting for any statistical analysis, that these must be combated The next stage is reached when endemic diseases, such as malaria, yaws, and schistosomiasis, loom large These diseases can be diagnosed either by inspection or by fairly simple microscopy Their incidence can be assessed by surveys, and there has been a tendency to permit the prevalence or absence of these diseases to obscure other parts of the health picture

For instance, the municipality of Singapore in the years 1935–40 was free from smallpox, cholera, and plague Malaria was well controlled and yaws and filariasis almost unknown It was therefore described in the reports as "healthy", or "remarkably healthy", though beriberi and tuberculosis were common, while the infant-mortality rate was over 150

In the absence of vital statistics, some information may be gathered from census figures, from sample areas, or from analogous conditions where statistics are available

The infant mortality is generally a fair index of the health of a community But the following figures from communities at three stages of development show that the disadvantages of bad conditions bear most heavily on children between the ages of 1 and 5

	Death rate	*Birth-rate*	*Infant mortality*	*Mortality in 2nd to 5th years*
England 1955	10	15	25	0 9
Jamaica 1948	13	31	86	13
Egypt 1947	22	38	205	49

Thus in Egypt in 1947 the total death-rate was only about twice that of this country in 1955, the infant mortality was eight times as high, but the toddler mortality was no less than fifty times higher It is the 1–4 age-group that is the most sensitive index

The contrast between the different countries can be expressed in a different way For instance, in Sweden less than 5% of the total deaths take place under the age of 5 years In Malaya, over 40% of the deaths are in the under 5's, and in Mexico nearly 50%

Records in villages in the Gambia and Tanganyika gives infant-mortality rates of 308 and 420 respectively From these we can get some idea of the enormous wastage of child life which is going on

It is impossible to overestimate the importance of this wastage In my experience it has a profound effect on the lives of the people A high child mortality creates severe stresses—physical, emotional, and economic It breeds fatalism and apathy In the overpopulated countries it is a most tragic and expensive method of population control

Surveys

In areas where vital statistics are not available, attempts have been made to assess health by surveys These have sometimes proved useful, but they can be misleading unless great care is taken to ensure that standards of comparison are valid

A survey is commonly conducted by a specialist in one branch of medicine or in one particular disease He may be well qualified to identify every case of leprosy, or trypanosomiasis, or eye disease, or schistosomiasis, but he is often unable to assess the importance of his specialty in the total health picture

In a survey the mathematical chances of meeting a chronic disease are, of course, very much greater than those of meeting an acute one In malaria, the blood may show parasites for many years, with leprosy or blindness people may survive 40 or 50 years, and diseases such as these may be recognised unfailingly But there is relatively little chance of seeing the diseases that mainly affect the children Gastro-enteritis may kill in a few days, respiratory diseases and acute beriberi may kill in a few hours t is often said that malaria is the agent chiefly respon- le for a high infant mortality, but it is hard to say ether the cause is not malaria plus malnutrition, which itself may be due to dyspepsia or recurrent enteritis ropean medicine has learnt to shun the double diag- sis, but in developing countries doctors must be pared to find a great complexity of diseases The exact nposition may show geographical and seasonal varia- ns, but it is not rare for children to have five or six ferent diseases at the same time A typical combination uld be malaria, ascariasis, beriberi, rickets, bronchitis, d scabies

Most surveys are ill equipped to observe the genesis d development of disease and very few have been nducted by pædiatricians Some depend on assembling e population in groups for inspection—when, in my perience, sick children are often left at home Though survey may give an idea of the extent to which mal- trition exists, it will seldom throw much light on the uses

Surveys by anthropologists and by social anthropolo- sts sometimes lead to constructive suggestions, but metimes merely to further surveys They are liable to ncentrate on one aspect of the problem It used to be ithropological measurement, more recently it has been e dream life or the sex life, the initiation rites, the other-child relationship, or the kinship pattern They ldom pay much attention to the part played by ill alth, or by menaces to health in determining human haviour If repeated surveys are carried out, and pecially if they are not followed by constructive action, ey may produce a sort of allergy and a non-cooperative mmunity In fact, surveys should not be lightly under- ken Much time and money can be wasted that would ave been better spent on improving permanent medical cilities for treatment and for observation

ecords and Histories

Sometimes useful information can be gathered from ospital or dispensary figures But these, again, must be reated with caution In one area it was found that only % of the deaths in hospital were in children under years of age, and yet in that area, half the total deaths vere in the under-5s Some hospitals do not give the age f the patients in their registers, so that without going hrough individual case-sheets one cannot find how many re children

Some observers have tried to collect information from ersonal histories, but these, too, can be misleading In ome areas women are anxious to prove their fertility nd will claim to have had more pregnancies than they have actually achieved In others the parents are unwilling to discuss the numbers of their children, for “ if we count them today, tomorrow they may die ” Again, others simply forget

In fact there is no short cut to assessment of status, needs, or resources Only by gaining the confidence of a people is it possible to discover either the facts or the attitudes and potentialities Even in countries where statistics are available their value must ultimately depend on the observer His experience, his powers of observation, and his diligence are the deciding factors in any form of assessment Many aspects of health cannot be expressed statistically But they cannot therefore be ignored

A Neglected Specialty

The primitive community depends on children for wealth and for survival More children mean a bigger, stronger tribe, more hunters, more field workers, more security for old age The primitive community also accepts as inevitable that perhaps half its children will die before maturity Nearly everywhere, except in certain overcrowded urban conditions, babies are welcomed with joy—but with little confidence

Medical departments have achieved spectacular success in controlling diseases, but improvements in the standard of living and of education have not kept pace, and too often child care has been neglected Disease control campaigns have led to a fall in the death-rates, but the birth-rates remain high, and a too rapid increase in population may jeopardise progress

Yet the countries, such as New Zealand, Scandinavia, and the United Kingdoms, which have the highest standards of child care and health, are not countries with high birth-rates It is only when people learn to have confidence in the survival of their children and pride in their future, that they begin to see the desirability of limiting their families to the number they can expect to look after properly

Efforts are being made in some places to encourage family planning But this cannot be forced upon a reluctant population even by the most totalitarian regime It must come as the result of improved parental responsibility It is through the maternal and child health services that responsibility can be encouraged and that birth-control techniques may be taught

In 1553 Sir Thomas Phaire[4] listed the diseases by which “ most commonly the tender age of chyldren is chiefly vexed and grued ” His forty-odd headings included·

> Stiffness of the limmes, watrying eyes, scabbynesse and ytche, canker of the mouth, streytnesse of the wynde, feblenesse of the stomake and vomiting, colyke and rumblyne of the guttes, fluxe of the belly, wormes, failynge of the skynne, chafyng of the skynne, leanenesse, lyse

The conditions among children in the developing countries today are better described in his book than they are in some books on tropical medicine, which sometimes give more attention to counting the hairs on the head of the mosquito, and the contours of the œsophagus of the larval nematode than to the disorders prevalent among the children

In many of the developing countries maternal mortality is high Early marriage, repeated pregnancies, and perhaps extensive female circumcision may lead to abnormalities and complications Sometimes these are due not so much to neglected obstetrics as to anæmia, malnutrition, malaria, and helminths In many areas women bear the burden of agricultural and laborious domestic work They may habitually carry heavy loads at every stage of pregnancy and of lactation As yet the effect of physical overwork on the incidence of premature labour, hæmorrhages, ruptured uterus, and failure of lactation has been insufficiently studied in fact the social aspects of midwifery need more attention But much is being done Maternity work is popular, obstetricians are often appointed, and in many countries there has been rapid progress in the training of midwives

The position as regards child health is much less satisfactory

In many of the developing countries there is little or no specialist care for children in wards or outpatient departments There is nobody to teach, advise, or supervise child care Even if international or other funds are available for treatment or research, there is no pædiatrician to devise suitable programmes

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[4] Phaire T Boke of Chyldren (Edited by A V Neale and H R E Wallis Edinburgh, 1955)

If a doctor is recruited who happens to have a special interest or qualifications in pædiatrics, he may not be given appropriate recognition, and may turn his attention to some subject offering better prospects As there is no hope of building up a special department, there is no continuity of staff Without continuity, research is restricted, records are poorly kept, follow-up is neglected, and progress is impossible

Some sections of reports on maternal and child welfare make no reference whatever to children Some mention that most of the children attending "well baby clinics" are in fact sick, but give no information about any treatment provided Hospital records rarely give the ages of patients, and even where there are children's wards there may be no cooperation between them and the welfare centres, and no follow-up

Welfare clinics may be under the jurisdiction of a medical officer of health who has little experience in pædiatrics and none in tropical pædiatrics Health visitors trained in Europe may know little of the conditions or the diseases of the area to which they are appointed Sometimes, being imbued with the idea that they should do preventive and not curative work, they turn away sick children or refer them to some medical assistant with little or no pædiatric experience Again, the welfare centres may refuse attention to children over the age of 18 months or 2 years, though the 1–4 age-group is known to be in great need of help Sometimes the health visitors are kept busy with maternity cases, or are given so little transport that they have small opportunity to visit in the homes

These are serious defects in the organisation of child health work There are places however where magnificent work has been done In the rural areas of Singapore Island the infant mortality was reduced from 267 to 90 in eleven years by a most efficient and appropriate maternal and child health organisation In Ilesha in Nigeria and in Vellore and other places in India the idea is being introduced that the children's clinics should be conducted from, and in close association with the children's departments in a hospital If such integration is more widely acccepted, it will lead to great improvement in child health, in nutrition, and in the standard of living Success will depend on the calibre of the pædiatrician and perhaps even more on the continuity of his appointment

The pædiatrician who goes to a developing country will find that he must be adaptable The type of work to which he has been trained in a more sophisticated region may have done little to prepare him for his new responsibilities

He will have to acquire a great deal of local knowledge of the position and work of women, attitudes towards the child, local traditions, food habits, and resources

He will find that instead of dealing with a few rare diseases, he soon has his clinics and his wards overcrowded with large numbers of very common diseases There is the problem of the multiple diagnosis, when the whole spectrum of disease may be new to him Necropsies may be difficult to obtain and laboratory equipment rudimentary

Few or none of the patients arrive with a doctor's letter, and the histories offered by parents may be unhelpful To the question "What is wrong with the child?" the answer may well be "A witch looked at him" or "A thunderbolt fell on him" Even the age of the child may be unknown

The pædiatrician may find that his staff knows very little about child health He must spend a great deal of time training, and teaching nurses and other doctors, and in organising record-keeping and follow-up In addition he may have to spend much energy on informing his seniors and superiors

Conclusion

A maternal and child health programme should be concerned with the care of the child, the whole child, and everything to do with the child, including the family It should include school health It is obviously one of the finest instruments for social medicine

Though children under 15 and their mothers may between them comprise over 70% of the population, the maternal and child health service is often looked on as a minor detail in the public-health programme But, whereas public health is geared to provide impersonal services, maternal and child health is essentially a service to individuals

If maternal and child health clinics are organised and supervised by a hospital, so that prevention, treatment, and follow-up can be integrated, they are likely to be far more valuable This integration means the continuing care to families, through episodes of sickness and health, in their problems of nutrition and behaviour, and at various stages of sophistication In this way medicine can become sufficiently flexible to give adequate and appropriate care to people with rapidly changing needs

At present too little attention is paid to child health in developing countries Pædiatricians are not much concerned with the tropics, nor are the tropical experts much concerned with pædiatrics, if we are to judge by the time spent on these subjects in the respective institutes In the United Kingdom teaching centres for undergraduates, postgraduates, and auxiliary workers could well teach more about child health, both clinical and social, and especially about the problems of the developing countries More short refresher courses, both in Europe and within the countries themselves, would be useful In research programmes more emphasis should be placed on long-term observation and less on short-term surveys and on laboratory investigations

Western, or scientific, medicine has much to contribute to international progress But its contribution will depend on its appreciation of the social sciences as well as of the biophysical, and it is perhaps through the balanced expansion of the child health services that its most important contribution can be made

We are continually reminded that life is short and art is long Life is indeed desperately short in some parts of the world, but art is not yet nearly long enough

I should like to record my debt to Dr H M M Mackay and to the late Prof John Ryle for the help they have given me I am also grateful to many people in many countries with whom I have worked, and with whom I have watched and discussed these problems Most of all I am indebted to my patients who ensured that I should become inevitably and intimately concerned with their social as well as with their clinical affairs

> " We have now described this disease as seen from within and then again from outside We know now the origin, the progress, and the outcome of the infection, as also the symptoms by which its presence is detected British medical skill seldom goes beyond that point in its research Once a disease has been identified, named, described, and accounted for, the British are usually quite satisfied and ready to investigate the next problem that presents itself If asked about treatment they look surprised and suggest the use of penicillin preceded or followed by the extraction of all the patient's teeth It becomes clear at once that this is not an aspect of the subject that interests them"—Prof C Northcote Parkinson, *The Pursuit of Progress*, p 102, London, 1958

SYMPTOMS AFTER CHOLECYSTECTOMY

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Most patients benefit from cholecystectomy, but symptoms continue or develop in 15–20% of patients after cholecystectomy for stones (Judd 1925, Weir and Snell 1935, Macdonald 1943, Mock 1953) Post-cholecystectomy symptoms are probably even commoner after cholecystectomy for non-calculus disease (Bettman and Lichtenstein 1937, Wilson et al 1936, Meyers et al 1939, Doubilet 1943) Erroneous diagnosis may lead to ill-advised operation (Gray and Sharpe 1944)

These unsatisfactory results have led to use of the term " post-cholecystectomy syndrome ", which seems to us unsuitable because in many cases symptoms precede cholecystectomy, and the symptoms are not constant enough to be regarded as a syndrome In some cases they are thought to be due to autonomic imbalance (" biliary dyskinesia "), and in others to cystic-duct remnants with inflammation or stone (Hicken et al 1947, Garlock and Hurwitt 1951) or neuromas arising from the original operation (Womack and Crider 1947, Troppoli and Cella 1953)

We have investigated the incidence and cause of post-cholecystectomy symptoms, and related these to the reasons for cholecystectomy

Investigation

Clinical Material

200 patients underwent cholecystectomy between January, 1950, and December, 1956, in one surgical unit in the Western Infirmary, Glasgow, none were operated on by either of us 141 were traced We could not contact the others, mainly owing to post-war population shifts, but examination of their records has shown no material difference from the group reported

The age at cholecystectomy varied from 20 to 79 (mean 57), 79% were aged 40–69 114 were women and 27 men

Plan of Investigation

The records were analysed, and 126 patients interviewed Each was asked for his view of the effect of the operation, and he was directly questioned about specific symptoms 15 other patients, who could not attend, answered the same questions by post The length of follow-up was over a year in all cases, over two years in 110, and over five years in 41 Those with significant symptoms were investigated

Results

Reasons for Cholecystectomy

134 patients (95%) had had definite severe pain before operation—either biliary colic or from acute cholecystitis

Of the 7 who had no pain, 2 had had intermittent jaundice, 3 had an incidental cholecystectomy at operation for pyloric stenosis or post-gastrectomy syndrome (case 17), and 2 had had flatulent dyspepsia with gallstones and a diseased gallbladder wall

At operation, the gallbladder was diseased in 106 (75%) cases, and contained gallstones in 129 (92%) It was never removed unless gallstones were present or the wall was obviously diseased In most cases both conditions were met The common bileduct was explored in 38 cases (27%), stones were found in 22

5 patients had secondary biliary-tract operations (table I)

Follow-up

The 141 patients have been divided into three groups

106 patients (75%) had been completely relieved of all preoperative symptoms

15 patients (11%) had been relieved of all pain, but on detailed questioning admitted to some symptom of biliary dyspepsia We felt that these were within the bounds of normal, indeed 4 considered themselves completely cured Since none suffered any disability, we considered these two groups together as 121 cases (86%) whose symptoms had been relieved by the operation

20 patients (14%) had significant symptoms after cholecystectomy

In 18 of the 20 patients with symptoms (table II), the cause was an extrabiliary lesion, most commonly peptic ulcer In only 2 cases (7 and 13) could symptoms be ascribed to the biliary tract

In cases 5–12 the presenting symptoms first appeared after cholecystectomy In only 2 cases (5 and 7) could the symptoms be attributed to the operation

Case 5 —A woman, aged 68, underwent cholecystectomy for biliary colic, dyspepsia, and jaundice Stones were found in the gallbladder, the common bileduct was not explored She was well for four years, then abdominal pain and vomiting began At laparotomy (since the follow-up interview) adhesions

TABLE I—SECONDARY OPERATIONS IN 5 CASES

Case no	Cholecystectomy		Time interval	Second operation			Result
	Preceding clinical features	Operative findings		Symptoms	Operative findings	Procedure	
1	Biliary colic, jaundice	50 pea sized stones in thick G B , dilated cystic duct, C B D normal	1½ yr	Rigors, jaundice, pain	C.B D dilated, no stones, no pancreatitis	Sphincterotomy	No symptoms after 7 yr
2	Biliary colic, no jaundice	One stone in distended G B , C.B D dilated, no stones in C.B D	9 mos	Rigors, jaundice, pain	C.B D 19 mm diameter no stones, ampullary stenosis	Sphincterotomy	No symptoms after 3½ yr
3	Slight jaundice, dyspepsia, pain, hepatomegaly	Chronically inflamed G B , C.B D dilated, no stones in C.B D , cirrhotic liver	10 days	None (postoperative cholangiogram suggestive of stone)	Inflammation head of pancreas	Nil	No symptoms after 3 yr
4	Biliary colic, dyspepsia, no jaundice	Single stone in thick inflamed G B , C.B.D not dilated	7 yr	Recurring jaundice	C.B D dilated, stone at lower end	Removal of stone	No symptoms after 1 yr
5	Biliary colic, dyspepsia, no jaundice	G B chronically inflamed with stones, C.B.D normal	4 yr	Attacks of epigastric colic and vomiting	Adhesions crossing pyloric antrum	Division of adhesions	Too early for assessment

C.B D , common bileduct, G B , gallbladder

TABLE II—ANALYSIS OF POST-CHOLECYSTECTOMY SYMPTOMS IN 20 PATIENTS

Case no	Sex	Age at cholecystectomy	Findings at cholecystectomy	Time interval after cholecystectomy (yr)	Cause of post cholecystectomy symptoms
					Presenting initially after cholecystectomy
5	F	68	Cholelithiasis	4	Post-cholecystectomy adhesions
6	F	30	Chronic cholecystitis, cholelithiasis	2	Gross obesity, chronic ill health
7	F	65	Thin gallbladder, multiple pigment stones	3	Pernicious anæmia, kinking of supraduodenal C.B D
8	F	54	Thin gallbladder, cholesterol solitaire	3	Diverticulitis
9	F	63	Chronic cholecystitis, cholelithiasis	1½	Post-hysterectomy pelvic discomfort
10	F	40	Cholelithiasis	1½	Migraine with bilious vomiting
11	F	54	Chronic cholecystitis, cholelithiasis, duodenal ulcer	3	Obesity, hypertension, angina, duodenal ulcer
12	M	61	Chronic cholecystitis, cholelithiasis	3½	Myocardial ischæmia, renal colic
					Continuing despite cholecystectomy
13	F	28	Acute cholecystitis, cholelithiasis, stones in C.B D	7	Probable stone in C B D
14	F	51	Chronic cholecystitis, cholelithiasis, hiatus hernia	5	Hiatus hernia
15	F	51	Thin gallbladder, cholelithiasis	3	Periodic vomiting of unknown origin
16	M	36	Subacute cholecystitis, cholelithiasis, duodenal ulcer	4	Duodenal ulcer
17	M	65	Thin gallbladder with one pigment stone, anterior Polya gastrectomy with efferent-loop adhesions	5	Post-gastrectomy efferent-loop syndrome
18	F	51	Cholelithiasis	5	Obesity, chronic nephritis
19	F	50	Acute cholecystitis, cholelithiasis	6	Psychogenic vomiting
20	M	52	Thin gallbladder, cholelithiasis, huge paraœsophageal hernia	4	Diaphragmatic hernia
21	F	42	Acute cholecystitis	2½	Duodenal ulcer
22	F	42	Cholelithiasis	3	Duodenal ulcer
23	F	54	Chronic cholecystitis, cholelithiasis, gastric ulcer	7	Gastric ulcer
24	F	62	Chronic cholecystitis, cholelithiasis	3½	Obesity, lumbodorsal osteoporosis

C B D, common bileduct

crossing the pyloric antrum were divided The biliary tree appeared normal Her symptoms have not recurred in the few weeks since operation

Case 7—A woman, aged 65, had a cholecystectomy for attacks of biliary colic and jaundice A thin gallbladder, with pigment stones, was removed, the common bileduct, which appeared normal, was not explored Severe addisonian anæmia developed, and responded to orthodox treatment She continued to complain of right hypochondrial pain Intravenous cholangiography showed a moderately dilated common bileduct (maximum diameter 15 mm), with no stone, but a kinking in the supraduodenal part of the duct—possibly caused by adhesions to the gallbladder bed

In cases 13–24 the term post-cholecystectomy syndrome is inapplicable because the symptoms were present before operation In some cases, cholecystectomy seems to have been justified since acute biliary symptoms were relieved In others, where cholecystectomy was done for symptomless gallstones, the original symptoms continued Only in case 13 were post-cholecystectomy symptoms referable to the biliary tract

Case 13—A woman, aged 28, had had severe pain with jaundice At cholecystectomy in 1950, acute cholecystitis with cholelithiasis was found, and one faceted stone and some mud were removed from the common bileduct Seven years after operation she has recurring attacks of upper abdominal and back pain with associated nausea, jaundice, and biliousness There is probably a stone in the common bileduct Intravenous cholangiography has shown a moderately dilated duct (maximum diameter 13 mm two years ago, 17 mm now) and suggests obstruction at the lower end of the duct

Extrabiliary Causes for Post-cholecystectomy Symptoms

Peptic ulcer—In 5 of the 20 patients, post-cholecystectomy symptoms were found to be due to peptic ulcer

At the primary cholecystectomy, gastrojejunostomy was done on 6 occasions for associated pyloric stenosis Symptoms of ulceration continued only in case 11 Cases 16, 21, and 23 had typical ulcer symptoms for a long period before operation, and they have returned

In case 17 the cholecystectomy, done during an operation for postgastrectomy symptoms, had no effect on them

Symptoms due to peptic ulcer can be very easily confused with those due to gallstones Peptic ulcer has been found in 5% (Bruce 1926), 11% (Meyers et al 1939), and 8·5% (present series) of patients submitted to cholecystectomy

Diaphragmatic hernia—In case 14, acute biliary symptoms were relieved by operation but symptoms of hiatus hernia continued Case 20 had a cholecystectomy and repair of a huge para-œsophageal hernia, this unfortunately recurred, as did mild symptoms identical with those present before operation The biliary symptoms did not recur

Other causes—Many patients were obese, and in 4 cases their symptoms were clearly due to such associated conditions as angina (table II)

Cases 15 and 19 had intermittent vomiting of obscure origin No organic cause has been found, and there is evidence that it is psychogenic in both cases

Post-cholecystectomy Symptoms Arising in the Biliary Tract or Directly due to Cholecystectomy

7 patients (5%) have had postoperative symptoms due

TABLE III—RELATION OF PREOPERATIVE SYMPTOMS AND FINDINGS AT OPERATION TO POST-CHOLECYSTECTOMY SYMPTOMS

Results	Preoperative symptoms			Findings at operation				
	Pain		Jaundice	State of gallbladder *			State of common bileduct	
	Present	Absent		Diseased wall and calculi	Diseased wall and no calculi	Normal wall and calculi	Dilated	Stones present
No symptoms (106 cases)	102	4	30	79	9	18	28	19
Minor dyspepsia only relief of acute biliary symptoms (15 cases)	11	1	2	13	0	2	2	2
Significant post-cholecystectomy symptoms (20 cases)								
(a) Extrabiliary (18 cases)	16	2	2	10*	1	6*	0	0
(b) Biliary (2 cases)	2	0	2	1	0	1	1	1
Total (141 cases)	134	7	36	103	10	27	31	22

* In 1 case with significant post-cholecystectomy symptoms due to extrabiliary causes the state of the wall was not recorded though there was a calculus

to either associated biliary-tract lesions or the operation In 4 patients the symptoms were relieved by a second operation (table I)

Stenosis of the sphincter of Oddi —Cases 1 and 2 had had successful transduodenal sphincterotomy for stenosis of the sphincter of Oddi with cholangitis The ætiology of this condition is not completely understood, dilators may or may not be responsible (Cattell and Colcock 1953, Brush et al 1955, Cattell et al 1957) The terminal intraduodenal portion of the common bileduct is very delicate, and tearing of the mucosa seems very likely to lead to fibrosis

Pancreatitis —This is not uncommon in association with gallbladder disease (Weir and Snell 1935, Love 1952, Walters 1956, Cattell et al. 1957) In our experience, the condition, if found at cholecystectomy, tends to settle down subsequently, but in case 3, at re-exploration ten days after the primary operation, an inflammatory mass was found to involve the head of the pancreas Exploration of the distal end of the common bileduct at the first operation may have resulted in localised pancreatitis from incidental trauma

Recurrent stone —At a secondary operation, seven years after cholecystectomy, stones were found in the common duct in case 4 Since the symptoms dated from a cholecystectomy (for acute cholecystitis) when the common bileduct was not explored, the stones were probably missed at the primary operation Case 13 almost certainly has a stone in the duct, and awaits operation

Conditions caused by operation —Adhesions arose in cases 5 and 7

Results Related to Reasons for Cholecystectomy

There was complete relief of symptoms in 102 (76%) of 134 patients who underwent cholecystectomy having presented with severe pain (table III) Only 2 now have significant symptoms due to biliary-tract lesions

36 patients had jaundice before operation, 30 (83%) of these are now totally symptom-free and only 2 have residual biliary symptoms of any consequence

We had intended to study patients with " biliary dyskinesia ", but we have been unable to find one We conclude that this condition does not arise where cholecystectomy is done for such reasons as in this series

No normal gallbladders were removed, but in 27 gallbladders (containing stones) the walls looked normal at operation (table III) 7 patients (26%) in this group had significant post-cholecystectomy symptoms—a rather higher incidence than in the whole series (14%) The symptoms were not due to disease in the biliary tract, except possibly in 1 case, but, since 1 in 4 in this group have had a poor result from cholecystectomy, it seems that, if a normal-looking gallbladder with stones is found at laparotomy, other lesions (which may be the cause of symptoms) should be sought

Intravenous Cholangiography

This was done in 13 of the 20 patients with significant symptoms The common bileduct was not displayed in 2 cases, in the remaining 11, no cystic-duct stumps were seen

The ducts were moderately distended (15 mm and 17 mm) only in cases 7 and 13 Dilatation of the common bileduct in man has not been found after cholecystectomy by us or other workers lately (Sandweiss and Fulton 1955, Hardie and Israelski 1956, Shehadi 1957)

Summary and Conclusions

The reasons for cholecystectomy have been examined in 141 patients, whose postoperative progress has been studied for one to seven years

No gallbladder was removed unless it contained stones or was obviously diseased

121 (86%) of the 141 patients were symptom-free after operation

Significant symptoms were found in 20 patients (14%), but, in all except 2, the causes were extrabiliary In 2 others, symptoms may have been caused by operation Symptoms due to biliary-tract lesions in 4 more patients had been cured before follow-up

No evidence was found of " biliary dyskinesia "

The use of the term " post-cholecystectomy syndrome " does not seem justified

We thank Prof C F W Illingworth for his interest and for facilities to make this study

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EFFECT OF CORTISONE ON DEVELOPMENT OF DIABETIC ACIDOSIS

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Because of the hyperglycæmic effect of adrenal steroids, there has been much interest in the role of the adrenal cortex in the development of diabetic keto-acidosis It has been suggested on the basis of animal experiment that activation of the adrenal cortex may be a consequence of insulin deprivation (McArthur et al 1954b) and in turn hasten the development of diabetic acidosis (McArthur et al 1954a) In man, on the other hand, it is clear that excess 17-OH steroids may induce (Conn et al 1948, Sprague et al 1949, Bookman et al 1953) or aggravate (Perera et al 1949) a diabetic state, and may be associated with insulin resistance (Sprague et al 1949), but rarely lead to keto-acidosis (Conn and Fajans 1956) Because of these apparent discrepancies between human and animal studies the present work was undertaken to study specifically the effects of excess cortical steroids on the development of acidosis in diabetic patients

Methods

8 patients, of ages ranging from 8 years to 65, were studied in hospital In 7 the diabetes was reasonably well controlled by diet and insulin, but in 1 (case 8) it was of the " brittle " type

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The patients fasted for thirty-nine hours (from supper of day 0 to 10 A M on day 2) during which time water was allowed ad libitum, but no insulin was administered Blood samples were taken at 9 A M and 9 P.M on day 1, and at 9 A M on day 2, and analysed for sugar, total ketones, CO_2-combining power, and, in case 8, esterified fatty acids In 5 patients an intravenous glucose-insulin tolerance test was done at the end of the period of fasting All the urine excreted during day 1 was collected and analysed for sugar, total nitrogen, creatinine, sodium, and potassium After an interval of three to seven days, during which the diet and insulin dosage were the same as those previously established, the experiment was repeated as before except that cortisone acetate was given by mouth in a dose of 50 mg every four hours beginning at 8 A M on day 1, and ending at 8 A M on day 2 (total 350 mg), the last dose thus being administered an hour before the glucose-insulin test

Ketones (β-hydroxybutrate, acetoacetate, and acetone) were measured by the method of Lester and Greenberg (1948), blood-sugar by that of Folin (1929), CO_2-combining power by that of Van Slyke and Cullen (1917), urine nitrogen by a semi-microkjeldahl procedure, sodium and potassium by flame photometry, chlorides by the method of Wilson and Ball (1928), creatinine by the method of Peters (1942), and serum-esterified-fatty-acids by the method of Bauer and Hirsch (1949) Intravenous glucose-insulin tolerance tests were performed by *giving an intravenous injection of 10 g* of glucose with crystalline insulin 8 units over a period of two minutes, blood was then obtained at twenty, forty, and sixty minutes after the injection The slope of the line relating the logarithm of the blood-sugar content to time was taken as an index of the response to insulin

Results

Cortisone caused an elevation in blood-sugar in all but 2 patients (cases 6 and 8) (figs 1 and 2) It had no consistent effect on ketonæmia or CO_2-combining power and did not alter the serum-fatty-acid content in the 1 patient in which this was measured (case 8) The effect on insulin responsiveness was variable (fig 3), it was diminished in 3 out of 5 patients

In accordance with many previous observations, cortisone resulted in variable increases in urinary excretion of nitrogen and potassium Glucose excretion was significant in only 2 patients during the control day of fasting, and cortisone produced a striking increase in both

Discussion

The development of diabetic acidosis is associated with increased urinary excretion of corticoids (McArthur et al 1950, Stowers 1951) Though some of this increase may be a renal phenomenon, related to the diuresis usual

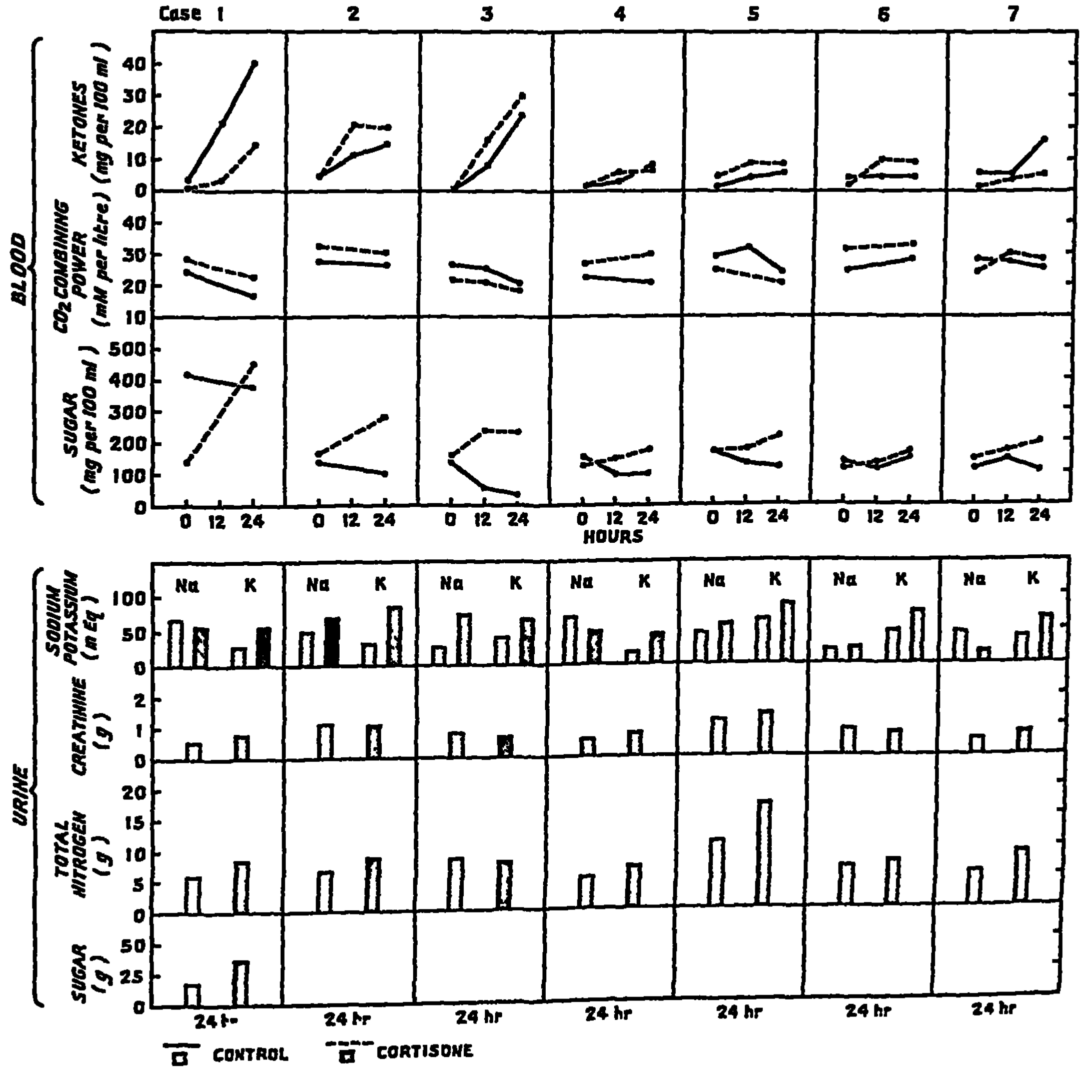

Fig 1—Metabolic effects of cortisone during fasting in 7 diabetic patients deprived of insulin Cortisone was given orally in a dose of 50 mg every 4 hours, beginning at 0, to a total dose of 350 mg

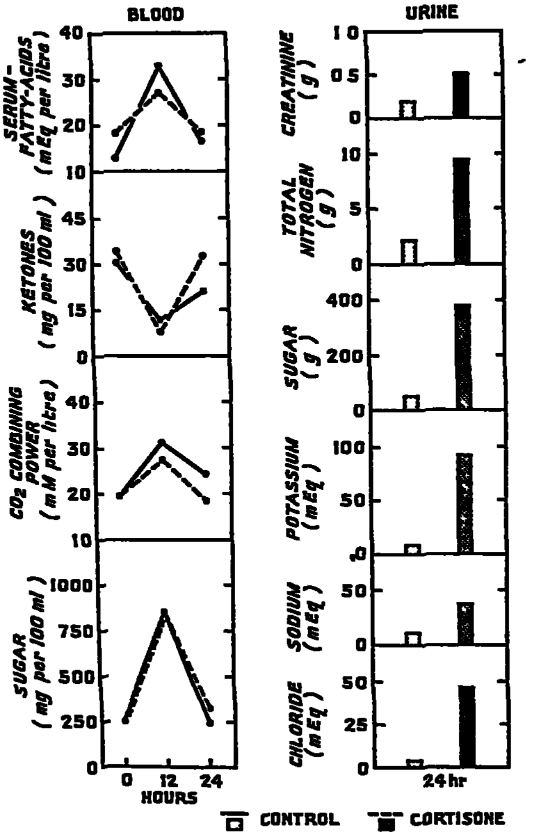

Fig 2—Metabolic effects of cortisone during fasting in a "brittle" diabetic patient (case 8) deprived of insulin. Cortisone administered as in fig 1

in the early stages of diabetic acidosis (Kalant 1955), the finding of elevated plasma-levels of free and conjugated 17-hydroxysteroids (Klein et al 1955, Wallach et al 1957) suggests that it is at least partly due to increased adrenal activity Subsequent work showed that in diabetic dogs stimulation of the adrenal cortex increased the severity of the tissue katabolism caused by withdrawal of insulin, and led to the conclusion that adrenal hyperactivity may hasten the development of diabetic acidosis (McArthur et al 1954a) Thus it was suggested that insulin lack was a "stress" which activated the adrenal, and the adrenal in turn aggravated the metabolic effects of the insulin deficiency

The present observations agree essentially with those obtained in dogs (McArthur et al 1954a) and show simply that the well-known effects of cortisone on tissue katabolism, electrolyte excretion, and insulin responsiveness are seen during development of acidosis as under normal circumstances Neither here in man, nor in the earlier work with dogs, was an increase in adrenal steroids shown to hasten the onset of ketonæmia or of acidosis (as manifested by a decrease in CO_2-combining power)

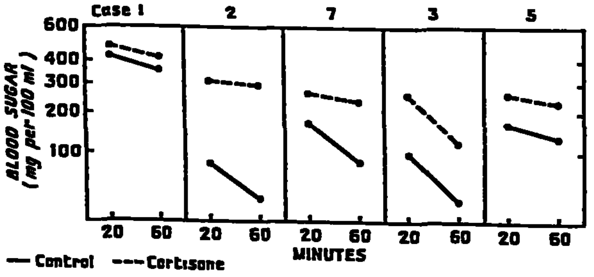

Fig 3—Effect of cortisone on insulin sensitivity in fasted diabetic patients. The slope of the line relating blood-sugar to time was determined after intravenous injection of glucose (10 g) and insulin (8 units), the greater the slope, the greater the insulin effect.

The lack of effect on acid-base balance may be due not only to the suppression of ketonæmia (Kinsell et al 1951), which is probably caused by increased peripheral utilisation of ketones (Kalant, unpublished), but also to the fact that the electrolyte disturbances usually produced by excess adrenal steroids result in alkalosis

A longer experimental period might have shown that, by causing hyperglycæmia and an increase in glycosuria, cortisone would hasten the depletion of body carbohydrate stores and so indirectly speed the development of ketonæmia. But even in case 8, where cortisone caused a very large excretion of glucose, there was no indication of more rapid production of acidosis

These observations suggest that adrenal cortical hormones should not be regarded simply as insulin antagonists, but rather that their overall effect in diabetes is a balance between anti-insulin action (increasing glycæmia and perhaps decreasing insulin responsiveness) and antiketonæmic, anti-acidotic action

Summary

Cortisone was administered to 8 diabetic patients during a twenty-four-hour period of insulin and food withdrawal, to determine its effect on the development of ketoacidosis

The steroid produced increased glycæmia, insulin resistance, and tissue katabolism, but did not increase ketonæmia or decrease the carbon-dioxide combining power

It is concluded that cortical steroids do not contribute significantly to the development of diabetic ketoacidosis

I am indebted to Dr F McCall and Dr E Harpur for permission to study patients in the wards of the Montreal Children's Hospital

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CHROMATIN-POSITIVE KLINEFELTER'S SYNDROME (PRIMARY MICRORCHIDISM) IN A MENTAL-DEFICIENCY HOSPITAL

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Low intelligence was found in some patients with Klinefelter's syndrome studied at a male-infertility clinic at this hospital (Ferguson-Smith et al 1957), the origin of these cases naturally excluded major mental defect A review of the published reports at this stage revealed several cases of oligophrenia associated with the syndrome, one of the original patients of Klinefelter et al (1942) was feebleminded and another unintelligent Pasqualini et al (1957) found 11 feebleminded among their 31 patients with Klinefelter's syndrome

In none of the previously published cases does the nuclear sex seem to have been investigated At the infertility clinic only patients with female nuclear sex showed significantly subnormal intelligence This suggested that a more severe degree of mental deficiency might exist in other cases Such patients would tend not to marry, far less to attend an infertility clinic, some might even require institutional care Accordingly, 325 mentally defective males at Lennox Castle Hospital were tested by the oral-mucosal smear technique of nuclear sexing (Moore and Barr 1955) I report here the results of this survey, including more detailed investigations of 4 patients found to have female nuclear sex The youth of 2 of these patients made it possible to draw further conclusions about the nature of the syndrome

TABLE I—NUCLEAR SEX AND GRADE OF MENTAL DEFECT IN 325 MALE MENTALLY DEFECTIVE PATIENTS

Group and grade of mental defect	Nuclear sex: Chromatin-positive (female)	Nuclear sex: Chromatin-negative (male)	No of patients
Partially selected sample			
Feebleminded	1	6	42
Imbecile	0	35	
Idiot	0	0	
Unselected sample			
Feebleminded	2	125	283
Imbecile	0	118	
Idiot	1	37	
Total	4	321	325

Methods and Materials

The initial group of patients was collected for me by one of the medical staff from among the ambulant patients, it was partially selected because he intentionally included an excess of patients thought to present clinical hypogonadism (table I) The discovery of female nuclear sex in case 4 (table II) prompted the study of further cases, taken from each of the main grades of mental defect but otherwise unselected This larger sample included 65 low-grade defective children from a branch hospital and 62 high-grade educable defective children, in the additional hope of discovering prepubertal cases of Klinefelter's syndrome The remainder consisted of the whole population of several male adult wards at Lennox Castle

An oral smear was obtained from each patient, and the degree of mental defect was recorded, no other investigation or examination was made except in the 4 cases with female nuclear sex, and in these only after this diagnosis had been confirmed Results of certain of these investigations are shown in table II No attempt was made to discover chromatin-negative cases of Klinefelter's syndrome (with male nuclear sex)

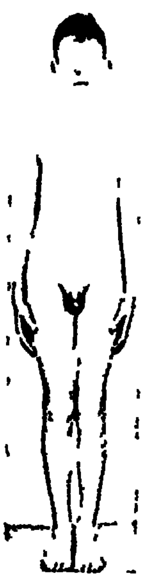

Fig. 1—Case 1, aged 14

Clinical Findings

Case 1 —A boy aged 14 (fig 1) was admitted in July, 1957, as a feebleminded person beyond parental control, with a mental age of 9½ years He is of average height and weight for his age but has particularly small testes and no development of secondary sex characteristics There is no gynæcomastia

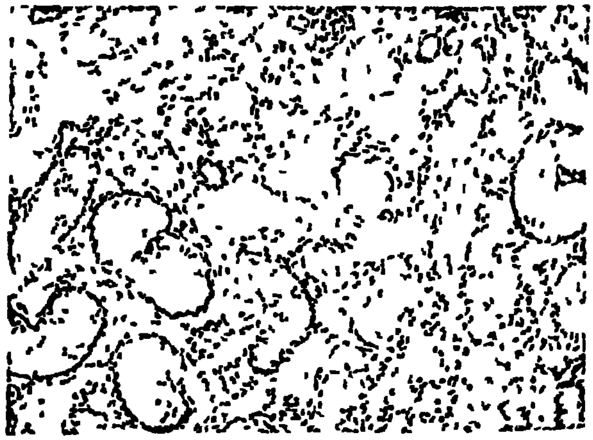

Fig 2—Case 1 testicular biopsy specimen showing numerous small completely hyalinised ghost tubules, scanty Leydig cells; occasional immature tubules lined by undifferentiated Sertoli cells; and complete absence of germ cells (Masson × 80)

Histology —Right testicular biopsy showed numerous small immature seminiferous tubules lined solely by undifferentiated

TABLE II—RESULTS OF SPECIAL INVESTIGATIONS

Case no	Age (yr)	Wechsler intelligence test: Full scale I Q	Wechsler intelligence test: Verbal I Q	Wechsler intelligence test: Performance I Q	Raven's matrices (1956)	Mill Hill vocabulary scale	Nuclear sex: Oral smear	Nuclear sex: 'Drumstick' neutrophils	Nuclear sex: Skin biopsy	Urinary excretion of hormones in 24 hr: Gonadotrophin (mouse units)	Total 17 ketosteroids (mg)	Œstrone (µg)	Œstriol (µg)	Œstradiol (µg)	Length of testis at biopsy (mm)
1	14	(67)*	—	—	Grade v (below 5th percentile)	Grade v	30%	6 118	Positive	20–40	5 2	1 5	Nil	3 7	18
2	14½	(<25)†	—	—	—	—	36%	6 637	"	—	—	—	—	—	30
3	28	52	66	52	Grade v	Grade v	34%	6 301	"	40–<80	25 3	4 7	Nil	Nil	22
4	52	66	64	72	Grade v	Grade II (below 25th percentile)	49%	2 1000	"	40	6·5	2 2	Nil	1 7	17

* Assessed by the Stanford Binet test † Low level of development prohibited more detailed assessment.

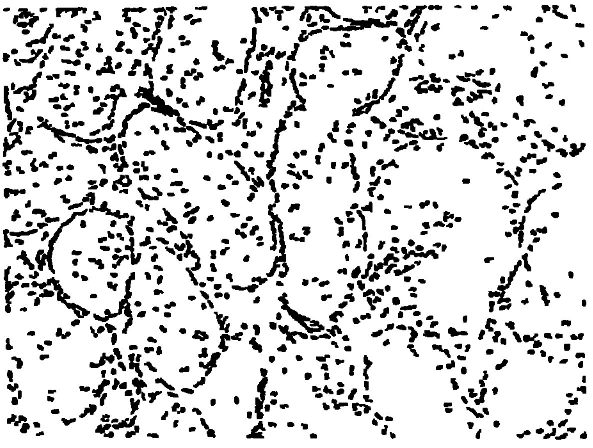

Fig 3—Case 2 testicular biopsy specimen showing immature tubules without germ cells (left) and several tubules showing scanty spermatogenesis (right), Leydig cells slightly increased and no hyalinisation of tubules. (Haematoxylin and eosin × 80)

Sertoli cells There were occasional small completely hyalinised "ghost" tubules, and Leydig cells could just be recognised In one tubule several spermatogonia and a few primary spermatocytes were seen Left testicular biopsy (fig 2) showed that a third of the tubules were small "ghost" tubules, Leydig cells were more obvious but not present in excess Sections stained by Weigert's elastic method showed a normal proportion of elastic fibres around the Sertoli-cell-lined tubules but a complete absence of elastic tissue in or around the small "ghost" tubules

Case 2—A boy, aged 14½, who was admitted at the age of 6 years, is an idiot, has frequent epileptic seizures, and is doubly incontinent His secondary sex characteristics are moderately well developed; his external genitalia are adolescent, and pubic and axillary hair are present. His testes are small There is no gynæcomastia

Histology—The histological appearances of testicular biopsy material (fig 3) were remarkable, most of the seminiferous tubules had no germ cells and were lined by Sertoli cells only No "ghost" tubules were found, and there was no evidence of any hyalinisation of the tubules A considerable proportion of the tubules (at least 20% of those in the right testis) showed active but scanty spermatogenesis to the spermatid level The number of Leydig cells was slightly increased

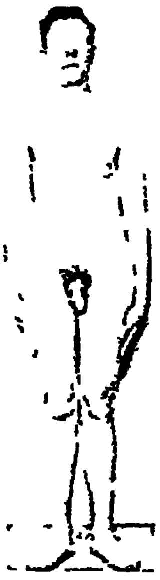

Fig 4—Case 3, aged 28

Case 3—A man aged 28 (fig 4) had been excluded from the ordinary school at the age of 11 years and had attended special schools, but his conduct was most unsatisfactory, and he was admitted to Lennox Castle as a feeble-minded person in need of institutional care He presented the typical features of Klinefelter's syndrome, with moderate bilateral gynæcomastia and small testes His prostate was impalpable

Histology—Testicular biopsy showed Sertoli-lined tubules among large aggregates of abnormal Leydig cells, most of the tubules were small "ghost" tubules identical in size and appearance with those seen in case 1 Scanty spermatogenesis, with maturation to spermatocytes only, was seen in two tubules A section stained for elastic tissue (fig 5) showed normal amounts around the Sertoli-lined tubules but none around the "ghost" tubules

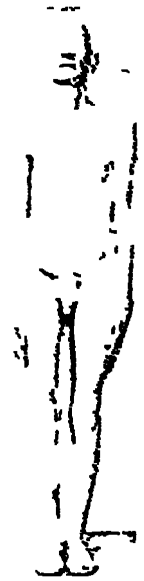

Fig 6—Case 4, aged 52.

Case 4—A man aged 52 (fig 6) had been involved in numerous homosexual incidents before admission to the Hospital at the age of 19 During the past twelve months he has complained of early fatigue and is losing weight His skin is smooth and soft, and there is general lack of body, facial, and axillary hair, definite slight bilateral hyperplasia of breast tissue is present, the testes are soft and small, and the prostate is impalpable The patient looks at least twenty years older than his actual age

Histology—Bilateral testicular biopsy showed an almost complete absence of recognisable testicular tissue Biopsy of his left testis showed only the hyalinised "ghosts" of tubules in an amorphous connective-tissue stroma, there were no Leydig cells Biopsy of his right testis showed a similar condition with the addition of a single small well-vascularised island of abnormal Leydig cells constituting the only sign of activity Weigert's elastic stain revealed two types of "ghost" tubules (1) most of them were small "ghost" tubules without elastic tissue, identical with those observed in cases 1 and 3, and (2) very much larger "ghost" tubules (fig 7) containing a considerable quantity of elastic tissue, and of about the same size as the Sertoli-cell-lined tubules in case 3 (fig 5), resembling the completely atrophic tubules commonly found at necropsy in the testes of elderly men In this case the diagnosis of nuclear sex from the blood-cells would have been misleading (table II)

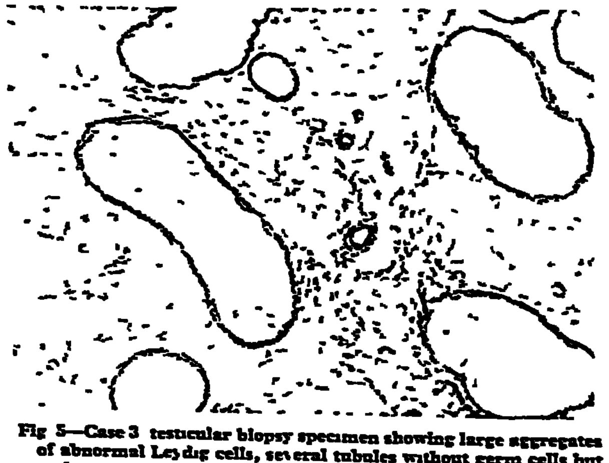

Fig 5—Case 3 testicular biopsy specimen showing large aggregates of abnormal Leydig cells, several tubules without germ cells but with normal amounts of elastic tissue and small ghost tubules with no elastic tissue (centre). (Weigert's elastica. × 80)

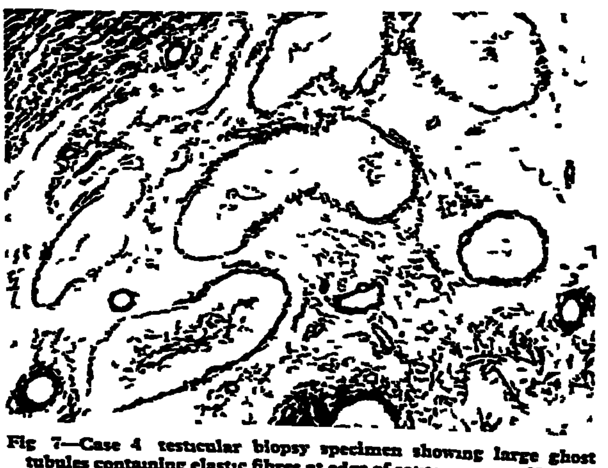

Fig 7—Case 4 testicular biopsy specimen showing large ghost tubules containing elastic fibres at edge of solitary mass of Leydig cells (lower right) Compare with fig 5 (Weigert's elastica. × 80)

Family Studies

The families of these 4 patients were investigated with particular reference to hereditary factors and to ætiological factors operating either during pregnancy or in early childhood No evidence of inheritance of Klinefelter's syndrome was found As is usual in such cases, an explanation of the disability was offered in each case

The mother of case 1 had active pulmonary tuberculosis during her pregnancy

The mother of case 2 conceived at the age of 43 and was treated during the first five months of her pregnancy with stilbœstrol and barbiturates in the mistaken belief that her symptoms were due to the menopause

It was claimed that case 3 was well until involved in a serious street accident at the age of 9 years

The mother of case 4 was aged 46 when she gave birth to the child prematurely after antepartum hæmorrhage

A family history of mental defect was found in case 1 only, the mother having two feebleminded stepbrothers There is a history of twins in the families of cases 2, 3, and 4 but none of the propositi is a twin, and at present there is no evidence to regard this as more than an incidental finding The relatively advanced maternal age at the time of conception in 2 cases, and the chronic illness during pregnancy in 1 other, are noteworthy in view of the hypothesis of Witschi et al (1951), who suggest that " blastophthoria " may be the primary cause of chromatin-positive Klinefelter's syndrome

Discussion

Incidence

It has previously been shown that patients with chromatin-positive Klinefelter's syndrome form 3% of all subfertile patients attending a male-infertility clinic (Ferguson-Smith et al 1957), and further calculations based on this material suggest that the incidence of these patients among the general population is at least 1 in 10,000 The present survey seems to indicate that the incidence is higher among mentally defective persons than in the general population Although the present series is too small to form the basis for a precise figure, it is not unreasonable to suppose that about 1% of male mentally defective persons requiring institutional care have female nuclear sex In fact, chromatin-positive Klinefelter's syndrome appears to be one of the commonest conditions associated with primary amentia yet described in males

Pathogenesis

In spite of its small size this series is important in relation not only to mental defect but also to the histogenesis of Klinefelter's syndrome

The great majority of previously published cases have been in young adults because, under normal conditions, it is only young adults who present themselves for investigation with this disorder (Nelson 1956) In the present series the oral-mucosal-smear technique of nuclear sexing as a screening test has led to the discovery of 2 younger patients and 1 older patient, and the testicular histology in these patients is especially interesting (But for this survey case 1 would have been considered to be an example of delayed puberty, and case 2 would have been entirely missed)

Certain conclusions may be drawn from examination of the testicular biopsies in these cases

(1) *The condition begins before puberty* —The hypothesis that a disturbance of Leydig cells at puberty causes hyalinisation of the seminiferous tubules and progressive atrophy of the germinal epithelium (De la Balze et al 1952) can no longer be held Although case 2 is postpubertal, no hyalinisation of tubules was found, and there was a complete absence of germ cells in most of the tubules In case 1, despite the prepubertal findings, completely hyalinised " ghost " tubules and a scarcity of Leydig cells were very striking features on left testicular biopsy The absence of elastic tissue in these " ghost " tubules may be taken as evidence that where the tubules degenerate they do so long before puberty The results of work in progress, extending the studies of De la Balze et al (1954), indicate that these elastic fibres normally appear in the tunica propria at about the age of 10 years Degeneration after this age, as in some of the tubules in case 4, produces larger " ghost " tubules with persistent elastic tissue (fig 7) Therefore treatment at puberty can no longer be expected to prevent sterility in adult life, because the germ cells are absent far earlier

(2) *Hyalinisation of the seminiferous tubules is not invariable in Klinefelter's syndrome* —Hyalinisation of the seminiferous tubules has long been considered to be characteristic, if not pathognomonic, of testicular biopsies in Klinefelter's syndrome Its absence in case 2 indicates that this is not an essential criterion and explains the relatively larger size of the testes in this patient

(3) *A considerable reduction in the number of germ cells appears to be the most significant defect* —Normally it is possible to identify spermatogonia in the supporting epithelium of the seminiferous tubules from a very early stage of embryogenesis, through infancy and childhood, up to the age of onset of spermatogenesis The scarcity of germ cells in these 2 younger patients suggests that there was either an initial failure of germ cells to reach the developing gonad during gonadogenesis or a selective destruction of germ cells at a later stage (but before puberty) The variable degree of damage to the tubules possibly supports the latter hypothesis Spermatogenesis is considered to be rare in Klinefelter's syndrome, therefore it is remarkable that it was found in 3 of the 4 present cases Maturation of germ cells was incomplete in each case, but mature spermatozoa have previously been reported in association with female nuclear sex in 3 cases (Bunge and Bradbury 1956, Nelson 1956, Ferguson-Smith and Munro 1958) The proportion of tubules showing spermatogenesis in case 2 (fig 3) is striking, and the theoretical possibility of fertility in such a person is not so remote as might previously have been imagined

(4) *Severe secondary testicular atrophy with premature senility may be superimposed* —Case 3 presents a hitherto undescribed appearance of one of the later stages of the natural history of Klinefelter's syndrome At a comparatively early age there was a complete failure of the gonads, with atrophy of the remaining tubules, which became large " ghost " tubules, and disappearance of Leydig cells, associated with symptoms of androgen deficiency

Although more cases must be studied before more definite conclusions can be drawn, it appears that the most significant change at puberty is hyperplasia of the Leydig cells Further surveys of the type described here will almost certainly reveal earlier stages of Klinefelter's syndrome and improve our knowledge of its pathogenesis

Nomenclature

Since the discovery that only some of the patients with Klinefelter's syndrome have female nuclear sex it is clear that the syndrome can no longer be considered to be a single entity and must be critically reassessed (Nelson 1957) Alternative names, such as " seminiferous tubule dysgenesis " (Grumbach et al 1957), " female pseudohermaphrodites with gonadal dysgenesis ", and " pseudomales " (Witschi et al 1957), are either insufficiently descriptive or may be misleading, none has any particular clinical significance

It has been found of practical value in this area (where 36 chromatin-positive cases have been discovered in the past eighteen months) to consider the classification from the clinical viewpoint The problem that presents is essentially the differential diagnosis of a patient with small testes—the one invariable finding in Klinefelter's syndrome Thus, all cases recognised in this way and showing no evidence of secondary testicular atrophy or of pituitary disease are classed as primary microrchidism and, on the basis of nuclear sexing, subdivided into chromatin-negative and chromatin-positive microrchidism

Sterility and microrchidism are constant features of the syndrome, variable findings include gynæcomastia, azoospermia, eunuchoidism, increased urinary excretion of gonadotrophins, and decreased excretion of 17-ketosteroids In view of the findings described here, mental defect and hyalinisation of the seminiferous tubules must now be added to the list of variable features, at least in chromatin-positive microrchidism

Summary

By the oral-mucosal-smear technique of nuclear sexing of 325 male patients at a mental-deficiency hospital were found to have female nuclear sex 3 were feeble-minded, and 1 was an idiot

Findings in 2 patients aged 14 are of especial interest as regards the pathogenesis of Klinefelter's syndrome

Primary microrchidism is suggested as a name for the condition

I am grateful to Dr Ronald C MacGillvray, physician-superintendent, Lennox Castle Hospital, for permission to publish and for guidance throughout the investigation, and to members of his medical and nursing staff, especially Dr J Campbell and Dr G L Ligertwood I am also indebted to Mr W S Mack for admitting the patients under his care and for the testicular biopsies, to Dr A B Telford Govan for the hormone assays, to Mr Andrew McGhie for intelligence testing, to Mr Norman L Russell for technical assistance, and to Mr G Kerr for the photomicrographs Cases 3 and 4 were reported at the Symposium on Nuclear Sex in September, 1957

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GASTRIC CANCER AND ATHEROSCLEROSIS

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In a series of papers Elkeles (1949, 1950, 1953, 1956) has pointed out that between gastric carcinoma and aortic calcification a certain relationship exists which may be of diagnostic importance According to his investigations peptic ulcer of the stomach is in a high percentage of cases accompanied by calcification of the aorta in elderly people, 64% of people aged more than 50 showing roentgenological signs of calcification, whereas patients of the same age-group with gastric cancer show much less or no calcification

Busch (1924) had already concluded that aortic sclerosis was less pronounced in cancer patients than in other people of the same age-group, and Casper (1932) corroborated this finding

Since gastric carcinoma is common in Iceland but arteriosclerosis is much less common there than in many other countries (Dungal 1936, 1953, 1955) we examined our necropsy material with a view to studying the relationship between gastric cancer and aortic sclerosis

Material

Since aortic sclerosis is only exceptionally seen in persons aged less than 50 in Iceland, and since other workers have mainly limited their statistics to persons aged more than 50, we decided to limit our quest also to those aged 50 or more In this age-group there were 1430 necropsies in 1934–56, including 149 cases of gastric carcinoma Since, however, the descriptions of the aorta were insufficient for our purpose in 320 cases, among which were 45 of stomach cancer, and 77 cases in which the description of the stomach and/or duodenum was insufficient, there remained 1033 cases containing satisfactory descriptions of stomach, duodenum, and aorta Of these 480 were in females and 553 in males

Classification

The condition of the aorta was classified into four stages 0, smooth, without intimal changes, +, atheromatous patches without noticeable calcification, ++, atheromatosis and calcified plaques, and +++, much calcification The results are shown in table I

TABLE I—GASTRIC CANCER AND AORTIC SCLEROSIS

Age (yr)	Sex	No of cases	Atheromatosis and calcification of aorta				Percent calcification (++ and +++)
			0	+	++	+++	
50–60	F M	11 20 } 31	7 14 } 21	4 6 } 10			
61–70	F M	18 29 } 47	4 14 } 18	7 9 } 16	6 6 } 12	1	38 9 20 7 } 27 7
71–80	F M	6 10 } 16	1 2 } 3	5	4	1 3 } 4	83 3 30·0 } 50 0
81–100	F M	4 6 } 10	1 2 } 3	1	1 2 } 3	2 1 } 3	75 0 50 0 } 60 0
Total	F M	39 65 } 104	13 32 } 45	11 21 } 32	11 8 } 19	4 4 } 8	38 5 18 5 } 26 0

Atheromatosis 32 3% Calcification 26%

In this table there are relatively many smooth aortas, not only in people age 50–60, where all are either smooth or showing slight atheromatous changes, but also in the older age-groups Even in the oldest age-groups (70 or more) there are people with relatively smooth aortas

Another striking thing in this table is the higher rate of calcification in women than in men Although the numbers are small, the lower rate of calcification at all ages in men and the total of 38% calcification in women against 18 5% in men indicate a definitely greater tendency towards calcification in women Compared with the fact that the incidence of gastric cancer in men is about double that in women, this may have some significance

Gastric Ulcer and Aortic Sclerosis

For comparison we listed all cases of gastric ulcer found in the same material and the condition of the aorta in these cases (table II) Gastric ulcers are rather infrequent in Iceland, in 3285 necropsies of patients of each sex we found only 94 (2 87 %)

Although the numbers are not large, they indicate that the incidence of atheromatosis is about the same as

TABLE II—GASTRIC ULCER (INCLUDING SCARS) AND CONDITION OF AORTA

Age (yr)	Sex	No of cases	Atheromatosis and calcification of aorta				Percent calcification (++ and +++)
			0	+	++	+++	
50–60	F	7 } 11	4 } 5	2 } 4		1	14 3 } 18 2
	M	4	1	2	1		25·0
61–70	F	4 } 12		2 } 5	2 } 4		50·0 } 41 7
	M	8	2	3	2	1	37 5
71–80	F	4 } 10		1	2 } 5	1 } 3	75 0 } 80 0
	M	6	1		3	2	83 3
81–100	F	4			1	3	100 0
50–100	F	19 } 37	4 } 8	5 } 10	5 } 11	5 } 8	52 6 } 51 4
	M	18	4	5	6	3	50 0

Atheromatosis 27 0% Calcification 51 4%

in cancer, but that calcification of the aorta is much more common (almost 100%) than in gastric cancer

Duodenal Ulcer and Aortic Sclerosis

Of duodenal ulcers we found only 17 cases, which showed the same aortic conditions as the stomach ulcers (table III)

Discussion

Our necropsy records are in agreement with those of Casper (1932), Elkeles (1949, 1953, 1956), and others, who found a considerably lower rate of aortic calcification in cancer cases

Elkeles (1956) found this not valid for lung cancer, although very pronounced for stomach cancer Neuburger (1930) found that carcinoma was but rarely associated with arteriosclerosis of the brain Wanscher et al (1951) also found considerably less arteriosclerosis in their necropsy material of 822 cancer cases than in 1013 control cases

Juhl (1955) investigated 12,355 necropsy records, of which 3725 were related to cancer, and found that aortic lesions were significantly less pronounced in the cancer cases than in the others, and this difference in calcification applied also to the coronary arteries Juhl suggests that cholesterol accumulates in the tumour and is consequently diverted from the arteries

TABLE III—DUODENAL ULCER AND AORTIC SCLEROSIS

Age (yr)	Sex	No of cases	Atheromatosis and calcification of aorta				Percent calcification (++ and +++)
			0	+	++	+++	
50–100	F	10	3	3	3	1	40 0
	M	7	2	1	2	2	57 1
Total		17	5	4	5	3	47 1

Atheromatosis 23 5% Calcification 47 1%

Casper (1932) also suggests *a direct causal relationship* between cholesterol metabolism and tumour growth and cites several workers, among them Borst (1924) and Jaffé and Eliassow (1927), who found that experimental tumours were easier to produce if the animals were fed cholesterin before and during the experiments

Roffo (1925) considered a disturbance of cholesterin metabolism as one of the determining causes which led to the imbalance terminating in cancer Elkeles (1956, 1957), on the other hand, interprets these facts as a diminished tendency to cancer in people with calcified aortas and thinks that cancer develops more easily in people with smooth aortas This explanation seems to be in better accordance with our findings We often find people aged 70 or more with smooth aortas, some with cancer and others without, whereas others of the same age-group have more or less severely atherosclerotic aortas, some with atheromatous ulcers It is unlikely that such changes would show retrogression due to mobilisation of cholesterol esters to a cancerous growth, and no such transfer has been reported

Our experience tends to confirm the explanation of Elkeles (1956, 1957), Busch (1924), and others that old people with smooth aortas are more likely to contract gastric cancer than are those with greater intimal changes Our knowledge of cholesterin metabolism is insufficient to offer a satisfactory explanation of this apparent causal relationship

Summary

In 1033 necropsies of people aged 50 years or more there were 104 gastric cancers A comparison was made between the condition of the aortas in these cases of gastric cancer and in controls of the same age (1) without cancer and (2) with ulcers In gastric cancer the incidence of atheromatosis was 32 3% and of calcification of the aortas 26%, against 31 3% and 47 3% in the controls and 27 0% and 51 4% in the ulcer cases

A causal relationship is assumed between cholesterin and calcium metabolism on the one hand and the development of cancer on the other

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ANÆSTHESIA FOR RAMMSTEDT'S OPERATION

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INFANTILE hypertrophic pyloric stenosis was not widely recognised until Hirschsprung reported 2 cases in 1877 Mack (1942) has described the evolution of its treatment Surgical treatment is now recognised as giving the best results, and the operation is the pyloromyotomy of Rammstedt (1912), which was based on earlier pyloroplasty procedures (Fredet and Dufour 1908, Weber 1910) This operation is one of the most successful in abdominal surgery, and in skilled hands a recovery-rate of about 99% is to be expected

Anæsthesia for Rammstedt's operation is still a matter of some controversy General anæsthesia is preferred by some (Page and Jewesbury 1937, Ladd et al 1916, Schaefer and Erbes 1918, Ladd and Gross 1950, Pasma 1954), and local analgesia by others (Levi 1911, Browne et al 1951, Black and Love 1957, Handfield Jones and Porritt 1957) The advantages and disadvantages of each method of anæsthesia are discussed by Black and Love (1957) I do not here intend to advocate one method to the exclusion of others, or to compare results obtained with different techniques, the series is obviously far too small for such a purpose Such comparisons (Cope 1918) have shown no significant difference in results attributable to the method of anæsthesia The choice of one or other method should depend more on the skill, preference, and ability of surgeon and anæsthetist than on the condition of the patient or on an arbitrary decision by either person

Material

Between January, 1949, and July, 1957, 150 patients with infantile pyloric stenosis were admitted to the United Oxford Hospitals and treated by Rammstedt's operation. 8 were operated on under general anæsthesia; in 6 of these 8 cases the anæsthetist concerned was more familiar with general anæsthesia than local analgesia for surgery of the newborn, and in 2 the diagnosis had not been established with complete certainty before operation. An uncertain diagnosis was regarded as a definite indication for general anæsthesia. 142 patients were operated on under local analgesia, and I intend to discuss the use of local analgesia for this operation and describe the technique that was followed. Local analgesia is preferred for two main reasons: (1) it causes less systemic upset, and (2) feeding is more rapidly re-established postoperatively and the risk of postoperative vomiting, due to the additional disturbance of a general anæsthetic, is eliminated.

In the 150 cases the proportion of boys to girls was 5:1; the distribution according to weight and age at the time of operation is shown in figs 1 and 2. The child aged 16 weeks was born 7 weeks prematurely. Eight surgeons performed the operations, but 90% of the patients were operated on by one of four surgeons. In every case the operation was carried out through a right upper trans-rectus incision.

Preoperative Treatment and Premedication

In the United Oxford Hospitals, all patients with infantile pyloric stenosis are admitted to the pædiatric wards, and the surgeon and anæsthetist are called into consultation by the pædiatrician at an early stage. The treatment is always surgical, and medical treatment with antispasmodic drugs is never tried.

The condition is not regarded as an acute surgical emergency, and a period of at least twelve hours for observation and assessment in the ward is allowed in even the fittest of infants who show no systemic upset. Should the child be seriously ill, with evidence of dehydration and alkalosis, this period of preoperative preparation is extended if necessary to correct the fluid and electrolyte balance. One very ill child was so deficient in chlorides on admission that he was having convulsions. These were stopped only by infusion of saline solution; attempts to control them with amylobarbitone sodium and paraldehyde had been unsuccessful.

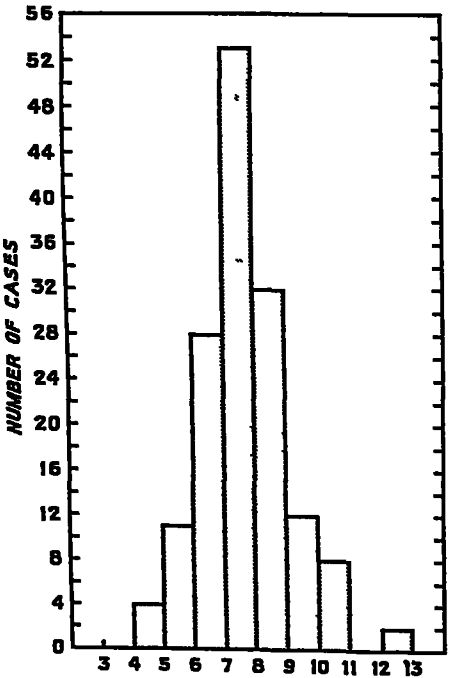

Fig 1—Weight-distribution of patients

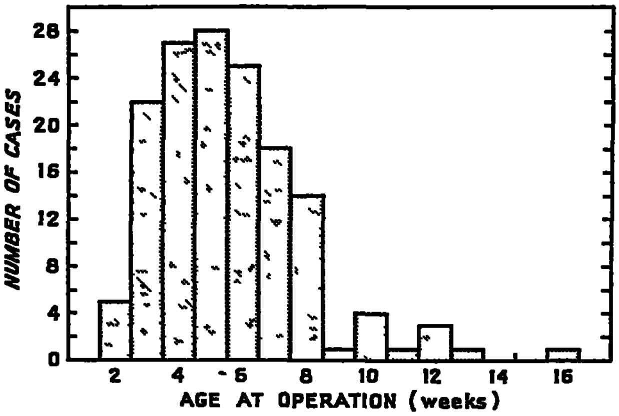

Fig 2—Age-distribution of patients

Although in this series the preoperative treatment was in the hands of the pædiatricians, this does not hold good in all hospitals. Anæsthetists are often directly concerned at an early stage with the treatment of these patients and the resuscitation of those who are gravely ill. An anæsthetist must, then, be fully conversant with all aspects of transfusion in infants. It is dangerously easy to overtransfuse a 7-lb baby.

An hour before the operation is to be performed, a rubber catheter (10 or 12 French) is passed through the nose into the stomach, which is washed out to remove any mucus or retained food. This tube should be left in position until after the operation. It prevents distension of the stomach with air—a condition that is a great hindrance to the surgeon—and is a safeguard against the regurgitation of stomach contents into the pharynx during the operation. Chloral hydrate is used for sedation and is given through the stomach-tube after the washout. It is administered as a mixture with the following formula:

Chloral hyd	gr 3
Syrup	minims 5
Aq anethi	ad 1 dram

Chloral produces its effect rapidly, since it is absorbed from the stomach, and it has a wide margin of safety. It was found advantageous to base the dosage of chloral on gr 1 per lb body-weight; such a dose quietened the child and had no dangerous depressant effects. The dose of chloral depends not only on the child's body-weight but on his fitness. In a few cases morphine gr $^1/_{80}$ (0·75 mg) was administered, but this practice was abandoned owing to the danger of respiratory depression. Atropine sulphate gr $^1/_{200}$ (0·3 mg) was given to all patients an hour before operation, except infants weighing less than 5 lb, to whom gr $^1/_{300}$ (0·2 mg) was given. No untoward reaction, attributable to the atropine, was seen in any child.

When the stomach has been washed out and the premedicant drugs given, the child is carefully bound on to a padded crucifix and left well covered in a room where the temperature is kept between 75° and 80°F until the time of operation.

Anæsthetic Technique

Since heat-loss in these patients must be kept to a minimum, the period for which the trunk is exposed for anæsthetic and surgical procedures should be as short as possible. The temperature of the anæsthetic-room and operating-theatre should be 75–80°F. Spirit should not be used to prepare the skin, and cetrimide solution

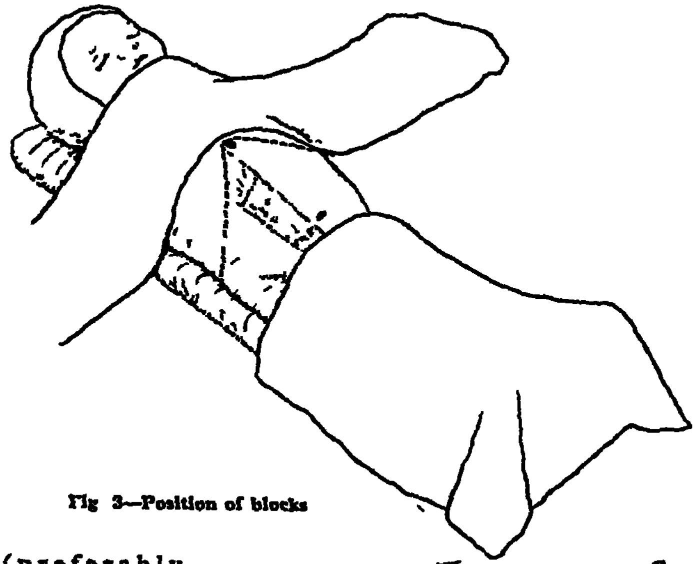

Fig 3—Position of blocks

(preferably warmed) can be advantageously used by both surgeon and anæsthetist

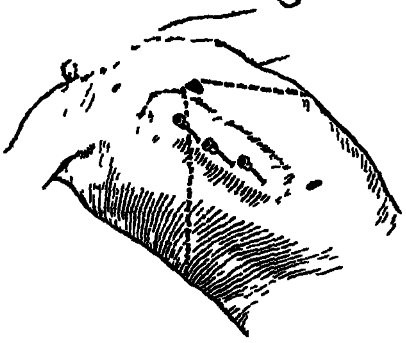

Fig 4—Area infiltrated

The area of infiltration and the blocks inserted are shown in figs 3 and 4 The subcutaneous tissues are infiltrated over the right rectus muscle from the umbilicus to a point above the coastal margin The three nerves supplying the right upper rectus muscle are blocked The tendinous intersections are intimately adherent to the anterior rectus sheath and may impede the flow of solution from one segment to the next The intersections vary slightly in position and in density of the fibrous tissue of which they are composed, and one or more may in fact be absent Since an upper right transrectus incision was used in all cases, no block of the left rectus was needed Altogether 10–12 ml of fluid is sufficient—2 ml for each block and the rest for infiltration

The drugs used were procaine, lignocaine (in nearly three-quarters of the cases), and cinchocaine (in 2 cases)

Because of possible toxic reactions to local analgesic drugs, some workers prefer general anæsthesia for Rammstedt's operation (Sington 1923, Hewer 1923), the risk of death ensuing from failure to adjust the dose of the drug to the weight of the patient was pointed out by Macintosh (1949)

The importance of using adrenaline in the solution and thus retarding absorption of the drug is often insufficiently emphasised Levi (1941) and Browne et al (1951) advocate the use of 0 5% procaine Levi, using a solution containing no adrenaline, regards 10 ml as a safe maximum volume Browne et al using a solution containing adrenaline, do not recommend the use of more than 15 ml Ward-McQuaid and Porritt (1950) use a solution containing 0 3% procaine with 1 600,000 adrenaline added, 15 ml of this solution contains 50 mg of procaine, which is a safe maximum dose for a baby of 7 lb, it is equivalent to 1 g of procaine in a 10 st adult, which is usually regarded as a safe upper limit for this drug Certainly the use of procaine in a strength of more than 0 5%, is unnecessary and dangerous

A solution of lignocaine 0 25%, containing 1/400,000 adrenaline, was used in most of the present cases and produced satisfactory anæsthesia 12 ml of this solution, containing 30 mg of the drug, is ample for a 7-lb infant, with a heavier patient the volume of solution can be increased proportionately, and with a smaller or a very sick infant the dose should be decreased

Ward-McQuaid and Porritt (1950), in their series of 100 cases, had 1 death due to procaine poisoning, 20 ml of 1% procaine without adrenaline (200 mg of procaine) was given Another patient had toxic reactions after infiltration with 25 ml of 1/1000 cinchocaine with 1/100,000 adrenaline, but this child recovered

2 babies in the present series had toxic reactions to the local analgesic drug (in each case lignocaine), in both cases the standard teaching on dosage of local analgesic drugs had not been observed, and the solutions used contained no adrenaline

An infant weighing 8 lb 11 oz, was given 12 ml of 1% lignocaine without adrenaline (120 mg of lignocaine) Convulsions and collapse followed in a few minutes and were controlled only by injecting thiopentone sodium via the jugular vein Oxygen was administered and the child recovered The operation was postponed for twenty-four hours and then successfully carried out under local analgesia using 0 25% lignocaine solution

An infant, weighing 7 lb 8 oz was given 20 ml of 0 5% lignocaine solution without adrenaline (100 mg of lignocaine) The operation was almost completed when convulsive movements of the face and limbs developed Again barbiturate was used to control the spasms and oxygen was administered The child recovered

These cases emphasise the importance of keeping the total dose of local analgesic below dangerous levels and of using a dilute solution The total weight of drug that may be safely injected depends somewhat on the strength of solution used, the more dilute the solution the slower the absorption of the drug into the blood-stream (Moore 1955) Adrenaline in the fluid still further delays the absorption, but the dose of this drug, too, must be kept as low as possible Dilutions of 1/400,000–1/600,000 are adequate, and stronger concentrations are both unnecessary and dangerous

Operation

Five to ten minutes should elapse between the final injection of local analgesic and the start of the operation, the more dilute the solution the longer it will take to exert its full effect During this period the child must be kept covered and warm If the operation is started too soon the infant can be quietened subsequently only by a general anæsthetic Before the infant is placed on the operating-table, the rubber mattress can usefully be warmed with a hot-water bottle

The use of a rubber teat containing cotton-wool soaked in a mixture of glycerin and dilute port or brandy is a time-honoured nostrum to divert the baby's attentions during the operation, but it can lead to swallowing of air if the content of the cotton-wool becomes exhausted This presents no difficulty if the stomach-tube has been left in situ, but it has been suggested that the use of a teat without a hole which has been dipped in the glycerin mixture still further lessens the tendency to aerophagy (I MacDonald personal communication) Since gastroenteritis is a serious complication of Rammstedt's operation, scrupulous attention must be paid to the cleanliness of the rubber teat and to the hands of the anæsthetist who is administering the mixture

The use of the catheter as a stomach-tube during the operation diminishes the risk of regurgitation of stomach contents into the pharynx owing to the surgeon's manipulations Regurgitated fluid can cause spasm of the larynx, particularly if the stomach still contains chloral—a substance which is very irritant to the larynx In 2 cases in this series, where the catheter was not left in the stomach, regurgitation of stomach contents produced laryngospasm that persisted alarmingly long On both occasions the operation had to be halted while the pharynx was aspirated and the child resuscitated with oxygen

Results and Discussion

There were 2 deaths in this series, both in patients who had been operated on under local analgesia

The 1st was a child, aged 8 weeks, who had been jaundiced since birth and had been admitted in the 1st week of life from a maternity hospital Pyloric stenosis developed while he was in hospital, and, although he was critically ill with steadily increasing jaundice, it was felt justified to operate on the pylorus in the hope that correction of one pathological process might improve chances of recovery from the other The operation proceeded satisfactorily, but the child died twenty-four hours afterwards At necropsy widespread necrosis of the liver was found, but the ætiology of this could not be determined This child died of liver disease and the pyloric stenosis was an incidental complication that had no real bearing on the fatal outcome

In the 2nd case, an infant aged 6 weeks, operation and the postoperative period were uneventful, and the child was discharged home on the fifth day A week after discharge an infection of the abdominal wound developed and the child was readmitted to hospital Gastroenteritis then developed and failed to respond to treatment, he died four weeks after operation This child would almost certainly have recovered if he had not been readmitted to hospital and exposed to the risk of cross-infection which caused the gastroenteritis

The mortality for this series is thus 1 3% It is, however, disturbing that failure to observe standard practice in the use of local analgesia nearly brought about 2 more deaths

Local analgesia does not provide satisfactory operating conditions in every case, in some it must be supplemented with light general anæsthesia, particularly when the abdomen is being closed Aird (1957) found general anæsthesia necessary in 1 case in 10 Of the 142 cases in this series operated on under local analgesia, 12 required general anæsthesia as a supplement Most of these 12 patients were anæsthetised by junior members of the department

Local analgesia, particularly when adrenaline is used in the solution, is regarded by some workers as inadvisable on the ground that it may impair healing of the abdominal wound and thus predispose to sepsis (Ladd and Gross 1950, Benson and Warden 1957) Of the present 142 patients operated on under local analgesia, only 3 had any sepsis and delay of healing of the wound, and in only 1 case was it necessary to resuture the abdominal incision

This series of cases follows chronologically on that published by Ward-McQuaid and Porritt (1950) They reported 11 deaths in 100 patients, and it is encouraging to note the improvement in results over recent years

Summary

Of 150 infants submitted to Rammstedt's operation 142 were operated on under local analgesia

Analgesia was induced by blocking the three nerves to the right upper rectus with, usually, 12 ml of a solution containing 0 25% lignocaine and 1/400,000 adrenaline 2 infants had convulsions when larger amounts were given

2 infants died—1 of unrelated liver necrosis and 1 of intercurrent gastroenteritis

I should like to thank Dr Victoria Smallpeice, physician in charge of the children's department, United Oxford Hospitals, for permission to quote from her records and for much advice and criticism, the surgeons, particularly Mr A Elliot-Smith and Mr A S Till, who operated on most of the cases, for their interest and assistance, Dr J V Mitchell for help in preparing this paper, and Miss Marjorie Beck for the illustrations

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STOKES-ADAMS ATTACKS TREATED WITH CORTICOTROPHIN

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There are at present few means of treating Stokes-Adams attacks Only adrenergic substances and atropine are widely used, and they often have no effect on the condition or produce only temporary improvement We report here sustained improvement following the use of corticotrophin in three cases of Stokes-Adams attacks which did not respond to conventional treatment

Case-reports

Case 1 —A Civil Servant, aged 35, had experienced occasional bouts of loss of consciousness since September, 1953, in which he became pale, had twitching movements of his limbs and face, and fell to the ground He had a premonitory sensation of precordial constriction Consciousness would return after ten seconds, and this was marked by flushing of his face and sweating He had had ankylosing spondylitis since 1940 He had no history of rheumatic fever On March 29, 1954, the attacks began to occur every fifteen minutes, and next day he was admitted to the Maida Vale Hospital for Nervous Diseases, where Stokes-Adams attacks were diagnosed Ephedrine had no effect on the frequency of his seizures, but on March 31 treatment with subcutaneous 1/1000 adrenaline 0 3 ml two-hourly was begun, and he improved When intramuscular adrenaline in oil 0 5 ml six-hourly was substituted, although he remained well initially, his pulse-rate fell and became irregular, and the attacks recurred On April 2, 1954, he was again given subcutaneous 1/1000 adrenaline, and the attacks ceased He had one further attack on the morning of May 3, 1954, when he was transferred to St Mary's Hospital

On examination his blood-pressure was 100/40 mm Hg and pulse-rate 46 His heart was not enlarged The first heart sound varied in intensity Electrocardiography showed complete heart-block with right bundle-branch block

Treatment and progress—Ephedrine gr $^1/_2$ t d s was given, the dose being gradually increased to gr $^1/_2$ four-hourly by May 11 Subcutaneous 1/1000 adrenaline 0 5 ml was added when his pulse-rate fell below 50 for as long as fifteen minutes This was given three times on April 24, although he had no attacks from the time of his admission until May 12, when he lost consciousness for a few seconds only He was feeling quite well again by May 13, but on May 14 he had two typical attacks with convulsions, and complete heart-block was again present, but during the preceding six weeks serial electrocardiograms had shown partial heart-block and, on two occasions, auricular flutter

Corticotrophin therapy—Treatment with corticotrophin gel 40 units b d was now begun, and after this there was no further attack The electrocardiogram returned to normal sinus rhythm after a short period of auricular fibrillation Ephedrine was discontinued and the corticotrophin gradually reduced On July 16, 1954, the patient was discharged symptom-free and in sinus rhythm on a maintenance dose of corticotrophin 15 units b d, which was finally discontinued on April 1, 1955

Follow-up—Although he remained free from symptoms, electrocardiography on May 26, 1955, showed a lengthened P-R interval and recurrence of right bundle-branch block Treatment with cortisone 100 mg daily was therefore started, but the electrocardiogram has not changed since that date The patient has been back at work since August, 1955 Cortisone was finally discontinued on Oct 25, 1956, with no ill effect

Case 2—A plumber, aged 45, had had rheumatic fever in 1931 at the age of 20 He had his first attack of loss of consciousness in 1936 and three further attacks in June, 1954 The attacks were preceded by a warm feeling, which spread from his epigastrium over the front of his chest to his neck and head He became unconscious after a few seconds and recovered in about a minute He noticed that his heart-beat was slow and forceful after an attack, and that he had sweated profusely He was seen at a hospital, told he had epilepsy, and given diphenylhydantoin sodium and phenobarbitone He was then free from attacks until Jan 13, 1956, when they returned with increased frequency, up to forty a day, often brought on by slight exertion It was now noticed that his pulse disappeared during the attacks He was transferred to St Mary's Hospital on April 26, 1956

On examination his apex-beat was six inches from the midline in the fifth space, a systolic thrill was felt at the aortic area, and a harsh systolic murmur was maximal here but conducted to the neck and apex, a diastolic murmur was conducted from the aortic area down both sides of the sternum His blood-pressure was 140/70 mm Hg There was no evidence of heart-failure Electrocardiography showed sinus tachycardia, a P-R interval of 0 2 sec, and left axis-deviation From April 28 until May 29, 1956, the number of attacks varied from one to forty-two a day, they were typical Stokes-Adams attacks in which the pulse and heart sounds were usually absent for about 25 seconds Electrocardiography showed that, at the start of an attack, the ventricular complexes ceased abruptly without any prolongation of the P-R interval The attack ended with the establishment of idioventricular rhythm in the presence of complete heart-block, which was followed by partial heart-block and the re-establishment of sinus rhythm

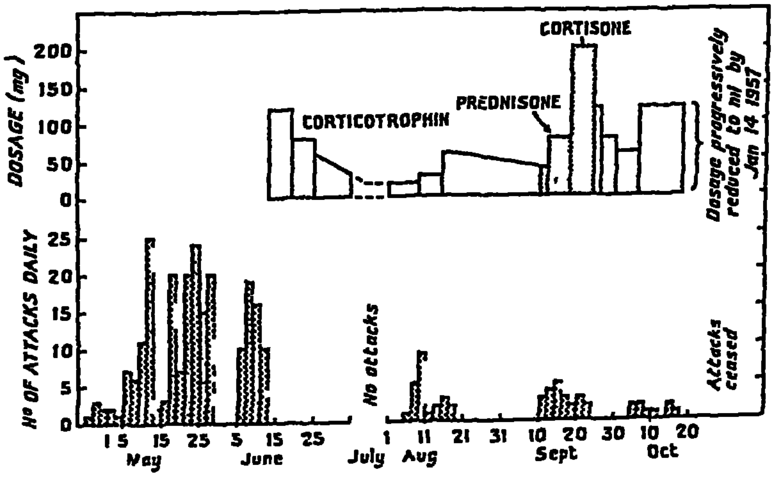
Treatment and progress—The number of attacks was apparently uninfluenced by adrenaline in oil 1 ml b d, ephedrine gr 1 q d s, methantheline 15–30 mg t d s, and atropine gr $^1/_{100}$ t d s From May 31 to June 7 there was no attack, stable complete heart-block having developed After a return to sinus rhythm on June 7 the attacks recurred and continued despite atropine gr $^1/_{60}$ t d s and digitalis folia gr $^1/_2$ t d s

Corticotrophin therapy was started on June 13, 1956, in a dosage of 30 units six-hourly, and the attacks ceased on that day The patient's response and subsequent progress are shown in the accompanying figure, which shows that the attacks recurred when attempts were made to reduce the dosage of corticotrophin, and that prednisone 60 mg daily and cortisone 200 mg daily did not control them The development of heart-failure on Oct 18, 1956, necessitated a reduction in dosage of corticotrophin until it was discontinued on Jan 11, 1957 Complete heart-block had developed on Nov 3 and continued until the patient was last seen in February No further attacks occurred until Feb 26, 1957, when he died suddenly

Necropsy findings (Prof D M Pryce)—The heart was enlarged, weighing 660 g, with healthy coronary arteries and valves except the aortic, which was narrowed and calcified and from which a calcified "buttress" extended into the ventricular muscle on the left side of the septum, near the bifurcation of the bundle of His Sections showed acute and chronic inflammation around the "buttress", which appeared to cross the bundle and its left branch The atrioventricular node was not involved

Case 3—A housewife, aged 35, was admitted to Ashford Hospital on Sept 20, 1956, complaining that in the preceding six weeks she had had at least ten attacks of faintness lasting several minutes She had noticed that lying down flat usually relieved the faintness, but on three occasions she had lost consciousness completely A week before admission sore throat with tender neck glands had developed There was a past history of growing pains and quinsies in childhood Her brother was said to have valvular disease of the heart

On examination she appeared intelligent and well but anxious Her throat was injected, and she had a subsiding herpes-simplex rash on her lips Her temperature was normal and her pulse basically regular, pulse-rate 80, but with frequent runs of irregular beats No other clinical abnormality was found Her blood-pressure during regular rhythm was 140/70 mm Hg Electrocardiography showed an auricular rate of 80 with a variable degree of auriculo-ventricular block and some dropped ventricular complexes, there was also right bundle-branch block The erythrocyte-sedimentation rate (E S R) was 17 mm in the first hour (Wintrobe), throat swabs were negative, and the antistreptolysin titre was less than 200 units per ml The level of uric acid in the blood was 3 mg per 100 ml, and blood Wassermann and Kahn reactions were negative *Cardioscopy showed nothing abnormal*



Corticotrophin therapy and progress in case 2.

Treatment and progress—During the first six days in hospital the patient had five attacks of faintness and nausea, and the irregularity of her pulse persisted On Sept 27 she had a long severe attack during which she was pale, cyanosed, and cold, sweated profusely, and had Cheyne-Stokes respiration The auricular rate was 100 a minute, and the ventricular beats were irregular at 10–18 a minute, occasionally coupled This attack did not respond to atropine, oral ephedrine, and isopropyl-noradrenaline, but after five and a half hours it was stopped by intramuscular ephedrine gr $1^{1}/_{2}$ During the next three days the patient was given oral ephedrine gr 1 and phenobarbitone gr $^{1}/_{2}$ eight-hourly and was well but for occasional palpitations and one brief syncopal attack Electrocardiography, however, confirmed the persistent presence of 2 1 heart-block, a P-R interval of 0 28 sec , and right bundle-branch block.

Corticotrophin therapy —On Oct 2, 1956, the patient had another long attack, similar to that of Sept 27 but with frequent periods of ventricular asystole accompanied by loss of consciousness and twitching On this occasion there was no response to intramuscular ephedrine She was therefore given intramuscular crystalline corticotrophin 40 units at 1 45 P M. At 6 P M her pulse-rate began to rise, the irregularities diminished, and her condition quickly improved By 8 P M 2 1 heart block was re-established, the ventricles beating regularly at 45 per minute The patient was now given corticotrophin gel 30 units twice daily, with a low-sodium diet and supplementary potassium, and from this time onwards she was symptom-free On Oct 3 the P-R interval was normal (0 2 sec) for the first time since her admission thirteen days previously By Oct. 4, 2 1 heart-block was abolished, and tracings made between Oct. 6 and Oct 12 showed the gradual elimination of right bundle-branch block. Sinus bradycardia (50 a minute) persisted until Oct. 19, seventeen days after the start of corticotrophin treatment The dose had by then been reduced to 10 units daily, and corticotrophin was finally discontinued on Oct 20 She remained well, with a normal pulse-rate, heart signs, and electrocardiogram until her discharge on Nov 3, 1956

Follow-up —She had had no recurrence of symptoms when she last visited the hospital, on July 15, 1957, though right bundle-branch block had returned for a short period and the E S R had remained raised

Discussion

Even in the untreated patient, the frequency and severity of Stokes-Adams attacks may change unpredictably, and spontaneous remissions are known to occur The success of any treatment is therefore difficult to establish Nevertheless it is unlikely that the improvement which followed corticotrophin therapy was due to chance in any of these cases

In case 1 an unstable cardiac rhythm of at least six weeks' standing was converted to a stable rhythm within six days of the first injection

In case 2 attacks which had occurred with a frequency of one to forty a day for many weeks stopped within a few hours of the first injection, and recurred twice when the dose was reduced

The attacks of syncope in case 3 were far less numerous but had been occurring for eight weeks, and electrocardiography during the last twelve days had consistently shown grossly abnormal conduction. The attacks ceased within six hours of the first injection and the electrocardiogram rapidly returned to normal

To these may be added a case published by Prinzmetal and Kennamer (1954)

Their patient, a man aged 60, had had numerous attacks of ventricular asystole for a week, following a posterior cardiac infarction Sinus rhythm was restored a few hours after a single injection of corticotrophin 40 mg , and a recurrence of heart-block a few days later was again abolished by treatment with corticotrophin After a ten-day course no further recurrence took place.

A very similar case has been reported by Phelps and Lindsay (1957), who used cortisone instead of corticotrophin

When the cause of a disorder is unknown, any discussion of the mechanism by which a method of treatment may influence that disorder must of necessity be speculative Corticotrophin was used in our three patients because it seemed possible that their heart-block was due to inflammation of the bundle of His

Case 1 had ankylosing spondylitis, a disease in which carditis is known to occur (Bernstein and Broch 1949)

In case 2 the presence of aortic stenosis of rheumatic origin suggested that the bundle might be damaged by a rheumatic lesion.

The origin of case 3's heart-block was more obscure, but her malaise, herpes simplex, and raised E S R. all pointed to infection as an underlying cause

In Prinzmetal and Kennamer's (1954) case corticotrophin was used in the belief that the inflammation at the periphery of an infarct might be interfering with normal conduction

The opportunity to confirm the diagnosis of inflammation arose only in case 2, where a cellular reaction with secondary calcification was found extending across the bundle from the diseased aortic valve This reaction could well have been inhibited by corticotrophin, but, if this is what happened, it is surprising that neither cortisone 200 mg daily nor prednisone 60 mg daily eliminated the heart-block. Possibly these doses were not large enough Opportunities to make similar comparisons between the effects of corticotrophin and adrenal steroids in cases 1 and 3 have not arisen

The improvement observed in our patients may have been due not to the suppression of inflammation but to an alteration in the metabolism of the heart-muscle which was favourable to conduction and contraction Such alterations have been postulated in Cushing's syndrome (Lown et al 1955) and during therapy with corticotrophin and with cortisone (Medical Research Council and American Heart Association 1955)

Hajdu and Szent-Györgyi (1952) have shown that, in the isolated frog's heart, deoxycortone can influence contraction and the state of the muscle between contractions, probably by a modification of ionic transport across the cell membrane, but it is difficult to draw inferences about human heart-block from the results of their experiments

The only direct evidence that heart-block may be influenced by metabolic changes is the observation that it can sometimes be abolished by infusions of molar sodium lactate (Bellet et al 1955, 1956, Swash and Wallace 1956)

In the treatment of refractory cases of Stokes-Adams attacks the choice between corticotrophin therapy and infusions of molar sodium lactate may be difficult Lactate infusions probably act more quickly, which could be a decisive advantage in some cases On the other hand, corticotrophin therapy avoids the need for an intravenous infusion and the considerable risks associated with the production of an acute rise in plasma pH Only further experience with both methods can determine their relative efficacy and safety The effects of the various adrenal steroids on Stokes-Adams attacks also merit further study

Summary

Three patients with severe Stokes-Adams attacks improved strikingly within a few hours of the start of corticotrophin injections They had all failed to respond to atropine and adrenergic drugs

We are grateful to Dr K D Keele for permission to publish case 3

References overleaf

PINK DISEASE AFTER APPLICATION OF MERCURY OINTMENT

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SINCE Warkany and Hubbard (1948) first described the high content of mercury in the urine of many children with pink disease, there has been much speculation about its exact importance in the pathogenesis of the condition

I report here the simultaneous development of pink disease in siblings who had been exposed, for a short period before the disease began, to identical sources of mercury

Case-reports

Case 1—A girl, aged 3 years and 1 month, was the first child of healthy parents She had never been given teething-powders or any medicine other than magnesia Early in December, 1955, she became irritable and, during the next three weeks, gradually lost her appetite and began to have screaming attacks during the night She lost about 5 lb in weight during this period At the beginning of January, 1956, her fretfulness increased, and she developed incontinence of urine and fæces Her hands and feet were extremely pink She was admitted to hospital on Jan 13, 1956

On examination she was thin and fretful, with no photophobia Her hands and feet were red, and one hand was peeling She had a follicular papular rash on her trunk Her pulse-rate was 122, blood-pressure 145/90 mm Hg, and heart normal There was no sign of infection in her throat, ears, chest, or urine Her inguinal glands were slightly enlarged Tendon-reflexes were all brisk and equal on both sides

Investigations—Examination of the blood showed Hb 104% (15 4 g per 100 ml), and white cells 6200 per c mm, neutrophil polymorphs 57% (3534 per c mm), lymphocytes 42% (2604 per c mm), monocytes 1% (62 per c mm) The serum-sodium level was 288 mg per 100 ml (125 mEq per litre), potassium 19 5 mg per 100 ml (5 mEq per litre), chloride 515 mg per 100 ml (88 mEq per litre) Radiographs of long bones, epiphyses, and abdomen were normal The urine contained a trace of albumin but no cells or casts, the pH was 6 0 160 ml of urine passed in twenty-four hours contained 112 μg of mercury

The patient was discharged home on Jan 21, 1956, and subsequently made a complete recovery

Case 2—A baby, aged 13 months, brother of case 1, had never been given teething-powders or any medicine other than magnesia Early in December, 1955, he became fretful, and this was attributed to teething Three weeks later his fretfulness increased, and he became limp and unable to sit up He also started to pull out his hair He developed a rash with pink hands and feet a week later than his sister His feeding and sleeping habits were not altered He was admitted to hospital with his sister on Jan 13, 1956

On examination he was well nourished but fretful, with no photophobia He was continually pulling at his hair He was sweating profusely, although his skin was cold His hands and feet were red and cold and covered with a maculopapular rash Apart from a napkin rash, the rest of his skin was clear His pulse-rate was 148 and blood-pressure 135/80 mm Hg His heart was normal There was no sign of infection in his throat, ears, chest, or urine, but his axillary and inguinal glands were slightly enlarged on both sides His tendon-reflexes were all present but diminished, and he had general hypotonia

Investigations—Examination of his blood showed Hb 92% (13 6 g per 100 ml), white cells 10,800 per c mm, neutrophil polymorphs 78% (8424 per c mm), lymphocytes 16% (1728 per c mm), monocytes 6% (648 per c mm) Serum-chloride level 547 mg per 100 ml (93 mEq per litre) Radiographs of long bones, epiphyses, and abdomen were normal 82 ml of urine passed in twenty-four hours contained 246 μg of mercury

The patient was discharged home on Jan 21, 1956, and has since made a complete recovery

Discussion

It was clear, from the urines of these two children that they had been exposed to a copious source of mercury For a long time all attempts to trace this source were fruitless, but finally, through the efforts of Mr M P Morel, the children's family doctor, the mystery was solved On repeated questioning the mother had always denied that any ointments had been applied to her children, but many months later she remembered that, in mid-October, 1955, another doctor had supplied an ointment, subsequently identified as ung hyd ammon *B P*, to be rubbed inside the anal margin and on the perianal region of the younger child each night as treatment for a possible threadworm infection This treatment had been continued up to the time of the child's admission to hospital The elder sister was extremely jealous of her brother and had insisted that she should have similar applications These had been given with equal thoroughness

Extensive inquiries did not reveal any other source of mercury to which the children might have been exposed

Pressure of medical opinion has led to the virtual disappearance of mercury-containing teething-powders, but children may still absorb dangerous quantities of mercury exhibited in other forms The prescription of any preparation containing mercury for children in the susceptible age-group should be avoided when effective alternative treatment exists

My thanks are due to Dr F S W Brimblecombe, under whose care these patients were admitted to hospital, Mr M P Morel, F R C S, for referring the patients and for solving the mystery of the source of the mercury, and Miss Margaret M McCready, B SC, for estimating the mercury in the urine

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SPONTANEOUS RUPTURE OF THE ŒSOPHAGUS AND BRONCHIAL ASTHMA

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SPONTANEOUS *rupture of the œsophagus, although rare, is being increasingly recognised during life* I report here two cases of spontaneous rupture of the œsophagus presenting with bronchial asthma within six months in a general medical unit This combination does not appear to have been reported previously

Case-reports

Case 1—A man, aged 32, an engineer by trade, was admitted to Saint Catherine's Hospital late on the night of April 25, 1957 He had had asthma since the age of 10 years He served with the R A F in the late war, both at home and abroad During this time he had little chest trouble, but since demobilisation in 1945 he had lived at home with his mother for twelve years in constant need of his isoprenaline spray

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He was rehabilitated in engineering in 1956 and took a job locally at which he was happy, and he was not troubled with asthma At Easter, 1957, he had noticed ankle swelling, which subsided with rest A few days before admission he had felt more tired than usual, but he remained at work Twelve hours before admission he started with an attack of asthma, and his condition deteriorated rapidly despite the use of bronchodilating drugs He became very dyspnœic and cyanosed He complained of no pain in his chest, had no nausea, and did not vomit Cough, which was minimal, produced mucoid sputum flecked with blood An hour before admission he became stuporose

On admission he was very distressed by dyspnœa He was a big heavy man and sat propped up in bed using his accessory muscles of respiration and perspiring freely Pulse-rate 120 and temperature 102°F Expiratory rhonchi were heard throughout both sides of his chest and crepitations at both bases There was no subcutaneous emphysema of his chest wall His blood-pressure was 120/80 mm Hg His abdomen was soft and not tender

Treatment and course—He was given intravenous aminophylline and intramuscular phenobarbitone sodium, and a four-hourly course of intramuscular penicillin and streptomycin was started No improvement took place in the next two hours, by which time his temperature had risen to 103 4°F His respirations became very rapid and shallow, with definite bronchospasm, cyanosis developed, and he appeared more collapsed Oxygen and further intravenous aminophylline were administered, and intramuscular cortisone was given but without any observable effect His condition deteriorated and he died at 8 A M the following morning

Necropsy revealed bloodstained turbid stomach contents in the left pleural cavity, acute inflammation on the pleural surface of the left lower lobe, emphysema of both lungs, sticky mucus in the bronchi, stomach contents in the œsophagus and pharynx, and a linear tear 1 inch long in the lower end of the œsophagus on the left side, through which the stomach contents were leaking into the left pleural cavity There was also a large tear in the cardiac end of the stomach, and stomach contents had escaped into the peritoneal cavity There was no evidence of ulceration of either the œsophagus or the stomach No other abnormalities were found

Case 2—A spinster, aged 45, was admitted to Saint Catherine's Hospital late on the evening of Oct 22, 1957 Apart from an operation on her nasal sinuses for " catarrh " the year before, she had had no illness in her life Three and a half weeks previously she had consulted her general practitioner, who thought she was starting with influenza, and advised her to go to bed Cough and wheeziness developed, which were not relieved by cough medicines She was off her food and remained in bed Concern was felt about her condition, and after a week a physician was called in consultation He noted intense generalised expiratory bronchospasm on auscultation Bronchial asthma was diagnosed, and tab 'Franol' and 'Iso-bronchisan' together with an expectorant mixture were prescribed For the next ten days the patient remained much the same, but she got out of bed for a while each day She slept badly, and during the night she was much troubled with coughing Two days before admission her dyspnœa got worse She had no pain in her chest and at no time vomited

On admission she appeared well built and sat up in bed using her accessory muscles of respiration She was dyspnœic, tachypnœic, and slightly cyanosed Examination of her chest revealed expiratory bronchospasm throughout both sides Her temperature was normal, her pulse-rate 100, and her blood-pressure 145/80 mm Hg She had no subcutaneous emphysema of her chest wall, and nothing else abnormal was noted on clinical examination

Treatment and course—She was given intravenous aminophylline, and a course of parenteral penicillin four-hourly was started Intramuscular phenobarbitone sodium was given, and later tetracycline therapy was started She became weaker and died at 9 30 A M the following morning

Necropsy revealed very sticky mucopus in the trachea and bronchi The left pleural cavity contained bloodstained stomach contents The lungs showed a sticky purulent bronchitis There was a linear tear of the œsophagus 2 inches long immediately above the diaphragm on the left side There was no ulceration of the œsophagus or of the stomach No other abnormalities were found

Discussion

Boerhaave first recognised spontaneous rupture of the œsophagus pathologically in 1724 Many reviews of this subject have been published in the last few years (Barrett, 1946, Ware et al 1952, Moynihan 1954, Anderson 1957) and more than two hundred cases have been reported In no case has rupture of the lower end of the œsophagus been described in association with bronchial asthma

The presenting symptoms are, in most cases, sudden onset of substernal, epigastric, or abdominal pain usually preceded or accompanied by vomiting Dyspnœa, shock, and cyanosis develop later, the dyspnœa resulting from the pain or from the development of a pneumothorax or a hydrothorax The earliest sign is said to be subcutaneous emphysema (Chamberlain and Byerly 1957) and has been reported in many cases Abdominal rigidity and tenderness occur, and signs of pneumothorax, hydrothorax, or pyopneumothorax develop later Bronchospasm has not been reported

The outstanding feature of the two present cases was the complete absence of pain and vomiting (in both cases details of the illness were checked with the relations after the necropsies) In case 1 there was a long history of bronchial asthma In case 2 severe bronchospasm was associated with bronchitis following influenza in an otherwise healthy woman

The ætiology of true spontaneous rupture of the œsophagus is unknown Many of the so-called " spontaneous ruptures " of the lower end are either postemetic or secondary to œsophagitis and ulceration which may have been symptomless A sudden increase in intra-abdominal pressure appears to be the precipitating factor in all cases and is the common denominator in rupture of the lower end of the œsophagus in pregnancy or labour, or associated with defæcation, strenuous exercise or epilepsy, severe vomiting, intracranial disease, or peritoneal irritation Cough is seldom associated with rupture of the œsophagus (Anderson 1957)

It seems likely that in both these cases, rupture of the œsophagus was secondary to raised intraluminal œsophageal pressure associated with severe wheezing and coughing From the two histories bronchospasm was unlikely to have been the presenting feature of the spontaneous rupture Published discussions of the differential diagnosis of spontaneous rupture do not include bronchial asthma

It is perhaps too much to suggest that spontaneous rupture of the œsophagus should be considered in a patient with bronchial asthma who has not responded to bronchodilating drugs There should be no delay, however, in such a situation in X-raying the patient's chest if the underlying lesion is to be detected Physical signs are obscured by the loudness of the expiratory wheeze The earliest sign of spontaneous rupture of the œsophagus on radiography is loss of translucency behind the heart, due to air escaping into the mediastinal tissues Today, when timely surgical intervention combined with antibiotic therapy can be lifesaving, it seems important not to miss this condition

I wish to thank Dr A Grunberg, under whose care these patients were admitted, for permission to publish, and Miss R Rawcliffe who performed the necropsies

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TETANUS

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THE successful treatment of a very severe case of tetanus with antitoxin and relaxing agents and by intermittent positive-pressure respiration in the presence of many complications is reported here

Honey et al (1954) were the first to report the treatment of established tetanus with tubocurarine and intermittent positive-pressure respiration, and were followed by Lassen et al (1954, 1956), Shackleton (1954), Smith et al (1956), and Ramsay et al (1956) The historical and therapeutic background of this treatment has been well covered by them and by Ablett (1956)

Knott and Cole (1952) defined six clinical types of tetanus and suggested that the severity of the disease tends to be inversely proportional to the length of the incubation period In the case reported here it was impossible to fix the incubation period, because the patient had two operations and a preoperative cut-down blood-transfusion, at any of which the infection may have taken place No swab taken from any wound on this patient at any time showed evidence of *Clostridium tetani* The incubation period may have been as short as eight days

Knott and Cole, however, further state that a more valuable measurement in assessing prognosis is the interval between the first symptom (usually trismus) and the first generalised reflex spasm, this may be termed " the period of onset " Usually, the longer the incubation period the longer is the period of onset, but, if there is any discrepancy, the period of onset gives a better indication of the probable severity of the tetanus As a guide to prognosis they suggest the following rule if the incubation period is more than seven days and the period of onset more than two days in an otherwise healthy patient, the chance of recovery is good On the other hand, with figures less than these the prognosis becomes rapidly worse

Case-report

A not very robust woman, aged 43, had bronchiectasis in her left lower and lingular lobes and her right middle lobe, On Jan 25, 1957, she underwent a dental clearance and on Feb 4, 1957, a left basal and lingular lobectomy Her convalescence was initially uneventful, though she ran a low-grade pyrexia from the third day and had been coughing up a good deal of bloodstained sputum Seven days after the operation, in the evening of Feb 11, she had backache and dysphagia By 6 A M on Feb 12 she had hypertonicity of the muscles of her neck and upper abdomen, and by 9 A M tetanus was diagnosed At 1 P M her rigidity had increased, and soon afterwards she had the first of two ' cyanotic attacks ", probably due to difficulty in swallowing saliva and pharyngeal secretions She therefore underwent tracheotomy under general anæsthesia with thiopentone, succinylcholine, and endotracheal gas-oxygen by controlled respiration A short right-angled cuffed tube mounted on a Magill suction T-piece was inserted into the trachea, and an œsophageal tube was passed into the stomach The thoracotomy, intravenous-drip, and drainage-tube wounds were explored and debrided

Day 1 (Feb 12)

The patient was given antitetanic serum 5000 units intramuscularly and 100,000 units intravenously and penicillin 1,000,000 units intramuscularly After the tracheotomy the patient quickly recovered consciousness, and sedation with intramuscular sodium phenobarbitone gr 3 six-hourly was started She also received small doses of pethidine intravenously from time to time From this time onwards, for thirteen days, she was kept continuously relaxed with tubocurarine and her lungs were ventilated by intermittent positive-pressure respiration Feeding through the œsophageal tube was begun with 3½ oz of ' Complan ' in 15 fl oz of water two-hourly Initially, respiration was effected by manual bag-squeezing through a Waters soda-lime canister, but later that evening the patient was connected to a Mortimer respirator She was ventilated with a mixture of 5 litres of air and 2 litres of oxygen

Day 4

Tubocurarine was continued in a dosage of slightly less than 10 mg hourly The patient's temperature rose to over 101°F Catheterisation initiated a bout of twitching During the removal of the endotracheal tube for cleansing, a bronchoscope was passed Little or no sputum was aspirated, but the endoscopy provoked generalised muscle twitchings During the night the patient was ventilated by continuous manual bag-squeezing, and apart from short periods the respirator was abandoned because its use seemed to be associated with an immediate accumulation of carbon dioxide

Day 5

Radiography showed that the patient's left upper lobe had partly collapsed, therefore vigorous two-hourly physiotherapy was directed to it, and the patient continued to be turned hourly from one side to the other

Day 6

The patient's temperature rose to 103°F Her right dorsal lobe appeared to be collapsed, so she was turned on to her face for about ten minutes for physiotherapy to this lobe aided by intratracheal suction Alarming distension of her abdomen appeared, so ' Sennokot ' was given through the œsophageal tube to initiate a bowel movement

Day 8

A Radcliffe pump lent to the hospital proved, with its ready adaptability to various respiratory rates and pressures, an enormous relief to the anæsthetic staff and apparently to the patient, who settled down well on this respirator Routine radiography showed an empyema in the left side of the chest Under local analgesia an intercostal catheter was inserted and connected to an underwater seal, and air blowing from the catheter confirmed the presence of a bronchopleural fistula Clinical examination suggested that the right lower lobe was collapsed, so, while the endotracheal tube was removed for cleansing, the vocal cords were sprayed with lignocaine 4%, and the patient was bronchoscoped This procedure made her cyanosed, and she required pure oxygen for half an hour afterwards until her pulse-rate settled down again During the evening her pulse-rate suddenly increased to 180 and an electrocardiogram showed auricular tachycardia Aminophyllin 0 48 g was given intravenously to relieve bronchospasm Acute paralytic ileus developed The distension of the bowel pushed the liver up against the flaccid right diaphragm and aggravated the collapse in the right lower lobe Much " coffee-grounds " fluid was aspirated through the œsophageal tube The patient was deeply unconscious, her hands became cyanosed, and her systolic bloodpressure fell to 50 mm Hg, indicating peripheral circulatory failure Her temperature rose to 104°F

Day 9

In the early hours the patient was apparently moribund, but a noradrenaline drip 4 mg per 500 ml of physiological saline solution was started at 60 drops a minute, and in the next twelve hours the patient improved dramatically 2 pints of blood was given Her temperature reached its peak of 106°F by the early morning, and cooling with wet sheets and electric fans was started

Day 10

The noradrenaline drip was discontinued after twenty-four hours, during which she had had 44 mg of the drug The dosage of relaxant during this period of severe illness was the lowest so far required in a day The paralytic ileus cleared up, and there was a general improvement in her lungs

Day 11

She began taking very small quantities of fluids by mouth Owing to her exhausted condition she required only 70 mg of tubocurarine in the twenty-four hours

Day 12

Her improvement was maintained Vigorous physiotherapy to her chest was continued. She showed signs of resisting the action of the Radcliffe pump, so, when the last dose of tubarine was wearing off, she was taken off the respirator for one to two minutes and encouraged to respire unaided She cooperated well in this, so we withdrew the relaxant, but after four hours without tubocurarine she had a major tetanic spasm

Day 13

Abdominal distension recurred, but gastric suction and intravenous dextrose and saline solution prevented ileus With the onset of distension the patient's right lower lobe collapsed again Her temperature rose to 102°F

Day 14

She received her last regular dose of tubocurarine After a second test withdrawal of relaxant there was no convulsion By the evening she could, with difficulty, open her eyes At this stage she still had hypertonicity and pain in the neck and intercostal muscles, and to overcome this she was given mephenesin 0 5 g two-hourly by mouth

Day 16

She breathed spontaneously for four hours The mephenesin was reduced to 0 25 g three-hourly, but neck rigidity was still severe, and the onset of increasing difficulty in inflating the chest caused us to revert to two-hourly dosage again, with good result Attempts to re-educate the swallowing reflex were made, but head retraction, neck rigidity, and the œsophageal tube hindered progress Attempts at swallowing caused saliva to appear in the tracheotomy wound

Day 17

A sudden increase in sputum necessitated bronchoscopy Since the patient's hæmoglobin was only 71%, she was given a transfusion of 2 pints of blood She was rather more restless and uncooperative, and we feared lest her cerebral cortex had suffered in the early cyanotic attacks, and we wondered whether we had been labouring so hard merely to keep alive a decerebrate

Day 18

The patient still required machine ventilation at times, as and when her own spontaneous respiration became rapid and inadequate

Day 19

She was still producing large amounts of sputum and was easily exhausted and worried by prolonged periods off the Radcliffe pump She would pass readily into tranquil sleep immediately after the start of artificial ventilation She was not easily roused to cooperation, and since she had had gr 197 of intramuscular phenobarbitone in twenty days the daily dose of this drug was immediately halved

Day 20

Lobar and segmental collapse still occurred rapidly and frequently The two-hourly regime of turning and physiotherapy was maintained The patient's spontaneous respiration was 40–44 a minute The œsophageal tube was removed after several successful attempts to swallow with the tube in place

Day 21

When the patient was breathing spontaneously through her tracheotomy, lack of humidification of inspired air seriously added to her difficulty in expectorating A Walley humidifier (Walley 1956) satisfactorily overcame this difficulty in a few hours This was the sixth day following the withdrawal of tubocurarine, and, though her tetanus was clearly cured, we were anxious at her continued drowsiness The appearance of athetotic movements aggravated our suspicions that she had had cerebral hypoxia Her appearance at this time is shown in the illustration, with the Walley humidifier in use All sedatives were discontinued this day The removal of the œsophageal tube seemed to have been premature, because further attempts at swallowing were not so successful as at first A sound sleep was ensured by putting the patient back on the Radcliffe pump for the night

Patient on 21st day wearing Walley humidifier

Day 22

The patient coughed more strongly now and produced sputum unaided

Day 23

She was still not swallowing sufficient fluids to maintain hydration and was therefore given two pints of $N/5$ dextrose and saline solution intravenously Her lungs were very much drier, aerating well at all areas Her mental state had also much improved She showed animated enjoyment of a radio programme which she heard through earphones She asked by signs for tea and successfully swallowed semi-solids

Day 25

She regained control of her bowels

Day 26

She recognised all the relations who visited her She slept throughout the night without the Radcliffe pump, which was not used again One of our difficulties at this stage was to determine when the swallowing reflex had recovered sufficiently to enable us safely to substitute for the cuffed tracheotomy tube a plain silver tube The cuffed tube seemed to accentuate the dysphagia, but the presence of food debris on top of the cuff appeared to us to be a definite contraindication to removal of the tube

Day 27

When the cuffed tracheotomy tube was temporarily removed on day 27 and the tracheostomy was occluded, the patient was able to phonate, repeating her name again and again She later confessed that her great pleasure at this achievement was because she thought she was never going to speak again

Day 28

She had partly regained control of micturition

Day 36

The tracheotomy tube was finally removed and the tracheotomy sinus allowed to close by granulation

Day 41

Skin was grafted on to her right foot under general anæsthesia because she had sustained a hot-water-bottle burn in the early days of her illness

May 22

The patient was discharged, having made a complete physical and mental recovery

Discussion

Prognosis

Based on the criteria of Knott and Cole (1952) prognosis seemed very poor The fulminating onset, the residual bronchiectasis, and the recent resection of lung were complicating factors Later she had an empyema and a bronchopleural fistula At one time or other almost every pulmonary segment collapsed A regime of antibiotics, three-hourly (and sometimes two-hourly) physiotherapy, postural drainage, bronchoscopy, and regular intratracheal suction prevented permanent atelectasis

Alimentary

Nutrition and hydration were maintained principally with complan $3^{1}/_{2}$ oz in 15 fluid oz of water three-hourly This volume was modified from time to time in the light of the patient's general condition

Relaxants

Tubocurarine was chosen as the relaxant because of its lack of side-effects, its length of action, its ease of administration, and its successful use in previously published cases Relaxation was carried to a point where the respiratory muscles were sufficiently atonic to permit the efficient exchange of gas by mechanical ventilation of the lungs The patient could often flex her wrists in spite of otherwise adequate curarisation, and we used this movement during her more lucid moments as a signal whereby she was able to respond to questions, using one wrist movement to answer " yes ", and the other " no "

Major tetanic convulsions were suppressed by curarisation, and none occurred from the onset until the twelfth day, when she was permitted to emerge from paralysis as a test of cure Generalised twitchings occurred when carbon dioxide accumulated, but these could be corrected, and it was not thought necessary to abolish them entirely Tubocurarine was given at all times through a Mitchell intravenous needle During the difficult transition period between complete relaxation with tubocurarine and the restoration of normal muscle tone, mephenesin was of great value in overcoming the painful hypertonicity of the neck and intercostal muscles

Respirators

After an initial period of manual ventilation the patient was connected to the Mortimer respirator on the evening of the first day Within forty-eight hours we had each independently decided that she was uncomfortable on this type of respirator Carbon dioxide accumulated quickly, but in our inexperience we may have contributed to this by giving inadequate doses of curare to allow the respirator to work effectively It was clear, however, that a smaller dose of relaxant was satisfactory when either manual ventilation or the Radcliffe pump was in use

The Radcliffe pump proved entirely reliable and easy to operate and had a conveniently wide range of speeds In the model lent by the manufacturers the suggested temperature setting of the thermostat in the humidifier produced droplets of water in the polyethylene tubes, so the setting was twice reduced, and finally the humidifier was used only intermittently Opinions varied on the desirability of using a negative phase in the respiratory cycle, and after a few days' trial it was discontinued, without apparent detriment to the patient

Inflation pressures varied between 18 and 25 cm of water The accumulation of carbon dioxide was indicated clearly and consistently by a sudden sharp rise in blood-pressure from the average of 120/80 mm Hg to 160/100 mm Hg or more, within two minutes of this sign the patient would begin to sweat profusely and then to twitch all over The soda lime was changed when on bag ventilation, or a further dose of tubocurarine allowed the respiratory muscles to relax sufficiently to clear the accumulation

For ventilation a mixture of air and oxygen was used principally (5 litres of air and 1 litre of oxygen), but at times it became necessary to use pure oxygen Nitrous oxide was not used at all, because Lassen et al (1956) reported severe depression of the bone-marrow after its prolonged use

Medication

Other workers have found chlorpromazine of value in treating milder tetanus Among its attributes is the freedom from excessive pharyngeal and bronchial secretions, which are common in tetanus Owing to gross infection in the present case we felt that the danger of liver damage contraindicated its use

Sedation was achieved initially with intramuscular sodium phenobarbitone gr 3 six-hourly and pethidine, but as the patient deteriorated she required progressively less sedation

Blood Chemistry

Estimations varied surprisingly little from the normal figures There was a tendency towards acidosis, and transient hypokalæmia came on during the gastrointestinal upsets All the estimations returned to normal after the resumption of spontaneous respiration

Humidification

During the first seven days, when ventilation was effected either by the Mortimer respirator or by manual bag-squeezing, the soda-lime canister acted as a very efficient humidifier While the Radcliffe pump was in use, the humidifier incorporated in the machine was used intermittently Humidification became a problem only when the patient was breathing spontaneously through the tracheotomy tube, and then the crusting of the secretions caused a deterioration in the condition of her lungs, which was rectified by the use of a Walley humidifier

Summary

Severe postoperative tetanus, complicated by bronchiectasis, empyema, bronchopleural fistula, and peripheral circulatory failure, was successfully treated with antitoxin, antibiotics, muscle relaxants, and intermittent positive-pressure respiration

The patient's complete recovery involved the full-time attention of anæsthetists for three weeks, and at all times the exceptional skill and enthusiasm of the nurses and physiotherapists

We wish to thank numerous friends and colleagues for their help and advice, especially Dr A Crampton Smith, of the Oxford respiratory unit, and Mr H G East managing director of East and Co , Oxford, from whom we hired the Radcliffe pump

References at foot of next column

Preliminary Communication

THE ACTION OF QUINIDINE INTERPRETED FROM INTRACELLULAR POTENTIALS OF SINGLE CARDIAC FIBRES

THE mode of action of quinidine has long presented a puzzling paradox. Lewis, Drury, Iliescu, and Wedd[1] originally claimed that quinidine prolonged the absolute refractory period of the dog's atrium, and, since the drug was also antifibrillatory, they considered that the evidence supported their view that fibrillation involved a circular sequence of excitation. Subsequently Love,[2] using a more precise method of measurement, found that the absolute refractory period was not, after all, prolonged by quinidine, but was sometimes shortened. The absolute refractory period of cardiac muscle is known to be approximately synchronous with the duration of the action potential,[3,4] and the latter also was shown not to be prolonged by quinidine.[5] The problem remained to explain how, when the absolute refractory period (i.e., the shortest interval after a stimulus at which a local response could be elicited by a second stimulus) was unchanged or shortened, quinidine nevertheless reduced the "effective refractory period", thus lowering the frequency at which propagated impulses could be conducted.

Recently developed techniques now enable more precise information to be obtained about the electrical activity of single cardiac fibres.

Fine capillary pipettes can be drawn with a diameter of less than 0.5 μ at the tip, and, filled with strong KCl solution, can be introduced into single cells to record potentials as efficiently as metal electrodes. When a microelectrode penetrates the membrane of a single atrial fibre, a negative potential of −75 mV is immediately recorded (the resting potential); during activity the potential swings rapidly positive to cross the original base-line and become positive inside the fibre relative to the outside by about +24 mV (the "overshoot"). The total rising phase takes about 3.0 msec. at 31°C, hence the average rate of rise is $\frac{75+24}{3.0}$=33 V per sec. The membrance then repolarises more slowly to its original value of −75 mV, reaching the half-way point in about 60 msec.

Simultaneous measurements of contraction, conduction velocity, and intracellular potential have been made in isolated rabbit atria in the presence of a wide range of concentrations of quinidine. The measurement of contractions permitted an independent estimate of toxicity, and it was found that concentrations of quinidine up to 10 mg. per litre did not reduce contraction by more than a quarter, usually by less. This agreed well with the direct measurements of serum-quinidine levels in man by Sokolow and Edgar,[6] who found that, in patients in whom atrial fibrillation was successfuly arrested, 75% of the levels were between 4 and 9 mg. per litre.

In the present experiments it was found that at concentrations of 10 mg. per litre or less there was no fall in the resting potential, and at much higher concentrations there was a reduction of only 2 or 3 mV. It was concluded, therefore, that the action of quinidine cannot be due to a change in resting potential. Again, at 10 mg. per litre or less, quinidine did not prolong the half-time for repolarisation and sometimes shortened it—which explains the absence of any change in absolute refractory period. The terminal phase of repolarisation was, however, prolonged (see below). In contrast, even at concentrations of 1–5 mg. per litre there was a great reduction in the rate of rise of the action potential and in conduction velocity. The height of the "overshoot" was also diminished.

These observations provide an explanation for the prolongation of the effective refractory period by quinidine in the absence of a change in the absolute refractory period.

It has been established[7,8] that a second propagated action potential cannot be elicited from cardiac muscle until the phase of repolarisation has proceeded to about two-thirds of the full resting potential—i.e., until the membrane has again become negative to about −50 mV in atrial muscle. A local non-propagated response can be obtained a little earlier, when the potential has reached only −42 mV; the absolute refractory period is thus a little shorter than the effective refractory period. In a normal atrium the duration of the terminal phase of repolarisation is consequently of no importance in determining the effective refractory period, because a propagated response can occur when the membrane has been repolarised to only −50 mV.

For a propagated response to occur, a certain minimum rate of rise of the depolarisation phase of the action potential is necessary, to overtake the process of accommodation. If the rate of rise is very slow, no propagated impulse can develop. It has been shown that the rate of rise is a function of the level of the potential of the membrane at which the action potential "takes off".[7,8] If a stimulus is introduced when the membrane is repolarised to −65 mV, the action potential takes off with a rate of rise much faster than if the stimulus occurs when repolarisation has proceeded only to −55 mV. As already stated, in a normal atrium the critical rate of rise for propagation can occur when the response takes off at about −50 mV. At −45 mV a local response can still occur, but the rate of rise is insufficient for propagation.

In the presence of quinidine the rate of rise itself was greatly reduced. The membrane had therefore to repolarise further before the critical take-off point was reached at which the rate of rise was fast enough for propagation. The duration of the terminal phase of repolarisation, normally unimportant, thus became significant in determining the effective refractory period. The absolute refractory period was unchanged, because the duration of the half-time for repolarisation was not prolonged by quinidine, and a local response could still occur at the normal point. But the rate of rise was so depressed that it was inadequate for propagation until repolarisation had proceeded much further than normal. The effective refractory period could, in fact, exceed the total duration of the action potential in the presence of quinidine. At high concentrations of quinidine the atria became totally inexcitable, although there was no significant fall in resting potential—i.e., the effective refractory period had become infinite, even though repolarisation was complete.

It is concluded that quinidine acts by affecting the phase of depolarisation, without necessarily prolonging the duration of the phase of repolarisation.

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Medical Societies

ROYAL SOCIETY OF MEDICINE

The Physician's Obligation to Society

THE *Section of Medicine met on* April 22 with Dr W A BOURNE, the president, in the chair

Looking back on the great demographic transformation which had taken place since 1750, Dr FFRANGCON ROBERTS described it as a unique event *in the history of* the human race which could never happen again To this change from high birth and death rates to low birth and death rates clinical medicine had contributed very little until the beginning of the 1914–18 war The main factors in this transformation had been the increase in national wealth and productivity that sprang from industrialisation, the ampler food-supplies generated by the agrarian revolution, and the general adoption of birth control Medicine did come into it, however, by taking part in the philanthropic movement of the 18th century and then in the important public-health measures of the 19th century Finally the present century had seen the harnessing of medicine to science and the doctor's involvement not only in curative work but also in social medicine He also found himself bound up in commerce, where advances in medicine, we must admit, largely resided

Thus, the doctor must now share in activities never dreamt of by his predecessors How had his obligations to society changed? Basically, not at all He still had his obligation to the individuals of whom society was composed, and since the end of the 18th century he owed an obligation to society to benefit individuals indirectly by improving social environment These duties were not so straightforward as they seemed, for doctors must consider the remote consequences of their actions—overpopulation, the ageing of the population, and a change in the balance of the sexes The conquest of malaria and yellow fever had been a triumph, but medicine could not advance further than food-supply Medicine was threatening to intensify the operation of the malthusian law and had indeed done so in some places This was a social and economic question, the doctor could only bring to bear his expert knowledge on contraception when he was asked to do so The ageing of the population brought a lot of unhappiness with it Again, the doctor's obligation, in Dr Ffrangcon Roberts' estimate, was limited to medical action, the social consequences as such were not his concern By the year 2000 England and Wales would contain 350,000 more marriageable men than women This was due to the saving of the lives of baby boys who, at birth, numbered 106 to every 100 baby girls At the other end of the scale lay the much greater capacity of old women to resist mortality, at age 60 and over, women would outnumber men by *2,000,000* Civilisation must therefore face the prospect of a world of compulsory bachelors being looked after by *widowed mothers*

The creation of the perfect environment was not the success some people *had hoped for* Neuroses in new housing estates and towns were three or four times commoner than in the old situations People became unhappy despite all efforts to make them happy Every stage in reducing mortality brought fresh difficulties we created problems as fast as we solved them

Dr E R CULLINAN interpreted the discussion's title as " to treat patients ", and what the patient wanted was to be cured with the least delay and discomfort, to get out of hospital quickly, to be told where he stood, and to get back as soon as possible to his usual life Only the profession could maintain the standard of the care it provided (its employers in the National Health Service could not do so), but to maintain the background he had learned in the teaching hospital the practitioner must be allowed time to do his work properly under good conditions

One of the most refreshing things in a teaching hospital was the diversity of interest among its staff One physician might be concerned only with the treatment of the sick, another with the study of disease for its own sake each must respect the other and they mostly did Some physicians combined treatment and research, and it was important that they should be clear at all times which they were doing—and that the patient should be clear as well Sticking needles and catheters into the patients in guise of treatment when what was done was really in search of knowledge seemed to Dr Cullinan very near to common assault

One of the patient's main needs was the knowledge and courage to adjust his world to his disability The cleavage between psychologists and physicians was still too wide, and it was clear that a sharp separation between organic and functional illness was no longer tenable All illness had some emotional content and all doctors were capable of listening to the patient's story, allaying anxiety if possible, helping him to adjust, and doing everything possible to see he had all necessary aid This was ordinary good doctoring The patient in hospital should be credited with intelligence and not regarded as an object or a disease (" the appendix in number 6 ") It should be explained to him that nurses and students were learning, which was why there was something always being done, such as the eternal smoothing of bedclothes Everything possible should be done to forestall the plea " I was told nothing "

When the patient left hospital his general practitioner should know all about him before he got home If he was not fit enough to go home, it was not just enough to say would you like to go to a convalescent home or to an old people's home? Did consultants, practitioners, and students know the labyrinthine network of ways in which the patient could be helped—the realm of the State, the local authority, the voluntary bodies? Could anything be done under National Health Insurance, or by the Assistance Board, the Ministry of Labour, or the local authority's many services? And could the patient benefit from any of the help offered by one of the many voluntary bodies? The patient could get into a sort of no-man's-land between different bodies, and the general practitioner should know what was happening and act as a sort of " humane umpire " all the time *In all this systemisation,* he might be the only remaining impartial adviser, bodily and even spiritually throughout the patient's life

Dr R R BOMFORD emphasised the physician's obligation to deal with the whole person and the total disability We often dealt relatively well with the patient's physical disease, but we made a mess of treating the patient as a person Dr Charles Newman, in his book, *The Evolution of Medical Education in the Nineteenth Century,*[1] had suggested that the new growing-point of medicine would be the understanding and control of the mind and of the mental aspects of all diseases Dr Bomford was prepared to argue that Freud had made the greatest contribution to clinical medicine in the past hundred years, because he had introduced a new clinical method—listening to the

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[1] See *Lancet,* 1957, i 411

THE LANCET

LONDON 3 MAY 1958

Safety in Prostatectomy

There have been three phases in the short but eventful history of prostatectomy On Dec 1, 1900, Freyer performed his first transvesical operation[1] He was not without his forerunners[2-4], but he was the first to prove beyond doubt that benign enlargement of the prostate constituted a surgical challenge He was soon joined in the fray by other pioneers, such as Rutherford Morison[5] and Thomson-Walker[6] in this country and Judd[7] and Young[8] in America, and by the end of the 1914–18 war the soundness of the operation was firmly established As is the common fate of bold surgical ventures, there followed a period of comparative stagnation and even of smugness The masters consolidated their technique, their teaching spread, the operation rapidly gained in popularity, but the mortality and morbidity rates remained unchanged For a new and still almost experimental form of surgery both rates were gratifyingly low, but, considering that the operation was undertaken for an essentially benign condition, these rates were not inconsiderable In the inauguration of the third phase Harris[9] played a decisive part His technical innovations were by no means dramatic, but he set out the details of his operation with unsurpassed clarity his step-by-step account of the management of patients could be followed by any busy general surgeon, and, most important perhaps, he turned his own, and he drew his colleagues', attention from the theatre to the ward By careful pre- and post-operative care prostatectomy was to become safe as well as sound

It has been said with much justice that " more patients die by the catheter than by the prostatectomy "[10], and it is therefore right that the catheter should have become the crux of surgical inquiry and dispute McEachern and his colleagues[11] at the Royal Adelaide Hospital advocate urethral catheterisation After decompression the catheter is tied in In cases of acute retention operation follows decompression at any convenient time within thirty-six hours, " a faster tempo than this is considered to be unsound practice, because there are too many important associated conditions which may be missed if the journey from receiving room to theatre is too short " Chronic retention is relieved by slow decompression, and if the blood-urea-nitrogen is over 40 mg per 100 ml—especially if this is manifest by uræmic symptoms—catheter drainage is continued under chemotherapeutic cover for seven to ten days McEachern claims that the dividends of this policy, both in lessened mortality and in shortened convalescence, have been gratifying, and statistical support for this claim is not wanting On the other hand, surgeons who prefer the suprapubic route of decompression, and those who reject any form of catheterisation as an unnecessary evil, can point to results which are at least equally good[12 13] and many would regard McEachern's management of chronic retention as retrograde " Slow decompression," Wells[14] said recently, " a sine-qua-non of recent days, is now, I presume, defunct It was based upon the theory that rapid decompression caused hæmorrhage and suppression of urine, complications now recognised as due to trauma and infection, or to electrolyte imbalance " Wells also criticised the facile acceptance of infection as an inevitable concomitant of stasis Autogenous infection of the bladder from the kidneys is certainly rare, and stasis per se does not lead to infection Only when stagnant urine is contaminated by catheter or by cystoscope does it become (and remain) infected With many practical obstacles barring the way to routine immediate prostatectomy, the risk of preliminary drainage may have to be accepted, but it remains a grave risk

Urethral catheterisation can lead to bladder infection in at least three different ways Organisms can be introduced by the catheter itself, and those who see this as the main danger prefer the indwelling catheter to repeated catheterisation Others picture the formation of a thin film of " culture-medium " between the catheter and the urethral wall—a broad highway rather than a free passage for organisms—and they recommend withdrawal of the catheter as soon as the bladder has been emptied Finally, the importance of intraluminal spread is shown by the reduced incidence of postoperative infection with the aseptic closed-bladder drainage[15 16] The provenance of the organisms is equally obscure Autogenous sources—the bowel and the traumatised prostatic bed—may account for some infections, but more and more evidence favours true cross-infection[17]

Unfortunately, catheterisation is still undertaken for no good reason far too often Acute retention can often be relieved by more homely and less dangerous methods, and to pass a catheter merely to measure exactly the amount of residual urine is the essence of meddlesome surgery

Abuse of antibiotic cover is so common that it would be surprising if this branch of surgery were exempt, the increasing proportion of resistant strains of *Escherichia coli* and *Staphylococcus aureus* isolated from specimens of urine after catheterisation need cause no surprise

In their operative technique McEachern and his colleagues differ little from surgeons in this country They approach the prostate by Millin's retropubic route[18] and follow Harris's method in the enucleation of the gland Like others, they have found chemotherapy no substitute for ligation of the vasa deferentia A rise in the incidence of osteitis pubis cast a cloud over the early history of Millin's operation, but McEachern

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[13] See *Lancet*, 1956, ii 343
[14] Wells, C *J R Coll Surg Edinb* 1957, 2, 120
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The claims of patients who seek operation for cosmetic reasons to be considered as truly in need of medical care are fully discussed To Gillies, a patient who needs a face-lift is a patient in need of medical help, and he operates on the mind through the face On the question of choice of operation for breast reduction, Gillies rightly draws attention to the advantages of the free graft of the nipple in elderly patients who need a major reduction Most patients who want a breast reduction are middle-aged, and not interested in two-stage procedures, they want a substantial reduction and an attractive breast form in one operation, and for most of them the free-graft method of Thorek is probably the best available today

A chapter is included on the difficult and controversial question of the surgery of sex conversion Here it is impossible to be dogmatic, partly because there is no generally accepted definition of sex There are different opinions about the appropriateness of operating on the external genitalia of people who ask for such operations Transvestites of either sex may be unsatisfactory patients, but it is unreasonable to deny that they are largely a medical responsibility, and Gillies has courageously accepted an aspect of this responsibility Valuable evidence can be expected from the later psychological outcome of his operations At the moment it seems that the adjustment to life of the "women" who are converted into "men" is better, in the sense of their becoming more stable and more reliable, than is the conversion of "men", mostly transvestites with homosexual tendencies, into "women"

Gillies has been specially fortunate in his co-author, Dr Millard, who devoted himself wholeheartedly to the enormous task of producing these concentrated volumes His own contributions to surgery are growing, and the merit of his work in Florida is widely recognised The book includes a chapter on anæsthesia by Dr Ivan Magill, without whose help in devising the necessary anæsthetic techniques for jaw and facial operations the specialty would never have developed as profitably as it has It is fitting that he should contribute to a book of historic importance, which must rank as one of the major surgical works in English of this century

The Doctor, His Patient, and the Illness

MICHAEL BALINT, M D, consulting psychiatrist, Tavistock Clinic London Pitman Medical Publishing Co 1957 Pp 343 40*s*

IN some medical schools, teaching about mental and emotional illness is still limited to a few lectures and to demonstrations of spectacular cases (Huntington's chorea, for example) Dr Balint rightly says that students are told to treat the whole patient, but are given little or no indication how to do so, which is unfortunate because much of general practice is concerned with emotional illness The untrained doctor may do harm as Dr Bomford observed at the meeting we report on p 944, the doctor-patient relationship may sometimes be pathogenic and very occasionally lethal Reassurance is often useless, and avuncular common-sense advice "is as limited and crude a tool as are carving-knife and screwdriver in surgery" On the other hand, there are good reasons for the deficiency most students are probably too immature to grapple with their patients' emotional difficulties, and there is little real knowledge about the treatment of whole patients that students can be taught

Dr Balint has organised seminars at which a group of family doctors and a psychiatrist discuss patients, their objects are less to help particular patients than to train themselves in psychotherapy and to research into the illnesses encountered and the treatments needed The group training can also help the doctor to achieve the personality change he usually needs, according to Dr Balint, to be a successful psychotherapist, for his personality determines his response to his patient and the treatment he gives The family doctor is well placed for such work Unlike the specialist, he sees the whole patient, whom he meets in many ways—as physician, obstetrician, psychotherapist, and family friend He sees the patient early in the illness when the prospects for preventive work are best, and unlike the specialist he is always available Most who have tried it find it a heavy responsibility but richly rewarding

Dr Balint's book is based on material gathered at these seminars It is really several books in one—an inquiry into the effect of the doctor on the patient (what he calls the pharmacology of the doctor as a drug), a plea for training in psychotherapy for suitable family doctors, a valuable source-book for anyone seeking to organise similar seminars, and a call for research into the pathology and treatment of the whole patient—which can be done only by general practitioners, and perhaps best through the type of meetings that Dr Balint describes

Everyone will take issue with some of his ideas, but there is so crying a need for research and training on the lines he advocates, and his book is so eloquent and modest a plea, that we hope it will be read by very many family doctors, psychiatrists, and teachers of medicine

Surgical Management of Pulmonary Tuberculosis

Editor JOHN D STEELE, M D, associate clinical professor of surgery, University of California School of Medicine Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1957 Pp 213 72*s*

THIS monograph is dedicated to the memory of John Alexander "with the affection, admiration and gratitude" of the thoracic surgeons he trained Similar monographs on other aspects of thoracic surgery will follow The surgery of pulmonary tuberculosis was Alexander's first interest—and the book on which he was working at the time of his death was to have had a similar title To produce a book which is a worthy memorial to a great figure is, however, far from easy and imposes certain limitations on editor and contributors which make repetition and stodginess hard to avoid In the circumstances original thought is scarcely to be expected and the authors have largely resorted to a historical review supplemented by a description of technique and an assessment of results The chief merit of the work, therefore, is as a historical document and in this respect its painstaking assiduity gives it a high standard It is beautifully produced and the illustrations and documentation are impeccable

In the future the book will no doubt be regarded as a monument to the era when thoracic surgery in tuberculosis was feeling its way towards the simple and effective solution ultimately provided by chemotherapy and resection The conviction grows in the reader's mind that such procedures as cavernostomy, plombage, even thoracoplasty, are almost bygones, mainly because of chemotherapy, and it is to the credit of the editor that he has included a comprehensive review of chemotherapy, so marking the settled position it has achieved in tuberculosis treatment

Alexander, one of the first to specialise exclusively in thoracic surgery, had a great influence on its development in the United States, and it is fitting that his merit should receive this unique tribute

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Current Therapy (Philadelphia and London W B Saunders 1958 Pp 781 84*s*)—Prof Howard Conn's annual is a little bigger and dearer this year, but it is a good investment for any hospital Its principal user will probably be the houseman who wants to know quickly the modern treatment for some emergency or some condition that is uncommon or out of his experience It would doubtless be impossible to compile a book of this sort to please everyone, but there is little here to quarrel with Some eyebrows will rise at the injunction to prescribe dihydrostreptomycin 4 g daily for 6–8 weeks in endocarditis, and at the choice of propylthiouracil in thyrotoxicosis

An International Symposium on Aldosterone (London J & A Churchill 1958 Pp 225 40*s*)—It is four years since aldosterone, the only adrenal hormone which seems free from pituitary control and plays a direct part in homœostasis, was isolated in crystalline form Last June the Clinique Therapeutique of the University of Geneva organised a symposium, under the chairmanship of Prof R S Mach, and attended by European and North American workers, the proceedings are here edited by Dr Alex F Muller and Miss Cecilia M O Connor

THE LANCET

LONDON 3 MAY 1958

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Michael Balint, M D, consulting psychiatrist, Tavistock Clinic London Pitman Medical Publishing Co 1957 Pp 343 40*s*

In some medical schools, teaching about mental and emotional illness is still limited to a few lectures and to demonstrations of spectacular cases (Huntington's chorea, for example) Dr Balint rightly says that students are told to treat the whole patient, but are given little or no indication how to do so, which is unfortunate because much of general practice is concerned with emotional illness The untrained doctor may do harm as Dr Bomford observed at the meeting we report on p 944, the doctor-patient relationship may sometimes be pathogenic and very occasionally lethal Reassurance is often useless, and avuncular common-sense advice "is as limited and crude a tool as are carving-knife and screwdriver in surgery" On the other hand, there are good reasons for the deficiency most students are probably too immature to grapple with their patients' emotional difficulties, and there is little real knowledge about the treatment of whole patients that students can be taught

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Everyone will take issue with some of his ideas, but there is so crying a need for research and training on the lines he advocates, and his book is so eloquent and modest a plea, that we hope it will be read by very many family doctors, psychiatrists, and teachers of medicine

Surgical Management of Pulmonary Tuberculosis

Editor John D Steele, M D, associate clinical professor of surgery, University of California School of Medicine Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1957 Pp 213 72*s*

This monograph is dedicated to the memory of John Alexander "with the affection, admiration and gratitude" of the thoracic surgeons he trained Similar monographs on other aspects of thoracic surgery will follow The surgery of pulmonary tuberculosis was Alexander's first interest—and the book on which he was working at the time of his death was to have had a similar title To produce a book which is a worthy memorial to a great figure is, however, far from easy and imposes certain limitations on editor and contributors which make repetition and stodginess hard to avoid In the circumstances original thought is scarcely to be expected and the authors have largely resorted to a historical review supplemented by a description of technique and an assessment of results The chief merit of the work, therefore, is as a historical document and in this respect its painstaking assiduity gives it a high standard It is beautifully produced and the illustrations and documentation are impeccable

In the future the book will no doubt be regarded as a monument to the era when thoracic surgery in tuberculosis was feeling its way towards the simple and effective solution ultimately provided by chemotherapy and resection The conviction grows in the reader's mind that such procedures as cavernostomy, plombage, even thoracoplasty, are almost bygones, mainly because of chemotherapy, and it is to the credit of the editor that he has included a comprehensive review of chemotherapy, so marking the settled position it has achieved in tuberculosis treatment

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Current Therapy (Philadelphia and London W B Saunders 1958 Pp 781 84*s*)—Prof Howard Conn's annual is a little bigger and dearer this year, but it is a good investment for any hospital Its principal user will probably be the houseman who wants to know quickly the modern treatment for some emergency or some condition that is uncommon or out of his experience It would doubtless be impossible to compile a book of this sort to please everyone, but there is little here to quarrel with Some eyebrows will rise at the injunction to prescribe dihydrostreptomycin 4 g daily for 6–8 weeks in endocarditis, and at the choice of propylthiouracil in thyrotoxicosis

An International Symposium on Aldosterone (London J & A Churchill 1958 Pp 225 40*s*)—It is four years since aldosterone, the only adrenal hormone which seems free from pituitary control and plays a direct part in homœostasis, was isolated in crystalline form Last June the Clinique Therapeutique of the University of Geneva organised a symposium, under the chairmanship of Prof R S Mach, and attended by European and North American workers, the proceedings are here edited by Dr Alex F Muller and Miss Cecilia M O'Connor

THE LANCET

LONDON 3 MAY 1958

Safety in Prostatectomy

THERE have been three phases in the short but eventful history of prostatectomy On Dec 1, 1900, FREYER performed his first transvesical operation [1] He was not without his forerunners [2-4], but he was the first to prove beyond doubt that benign enlargement of the prostate constituted a surgical challenge He was soon joined in the fray by other pioneers, such as RUTHERFORD MORISON [5] and THOMSON-WALKER [6] in this country and JUDD [7] and YOUNG [8] in America, and by the end of the 1914–18 war the soundness of the operation was firmly established As is the common fate of bold surgical ventures, there followed a period of comparative stagnation and even of smugness The masters consolidated their technique, their teaching spread, the operation rapidly gained in popularity, but the mortality and morbidity rates remained unchanged For a new and still almost experimental form of surgery both rates were gratifyingly low, but, considering that the operation was undertaken for an essentially benign condition, these rates were not inconsiderable In the inauguration of the third phase HARRIS [9] played a decisive part His technical innovations were by no means dramatic, but he set out the details of his operation with unsurpassed clarity his step-by-step account of the management of patients could be followed by any busy general surgeon, and, most important perhaps, he turned his own, and he drew his colleagues', attention from the theatre to the ward By careful pre- and post-operative care prostatectomy was to become safe as well as sound

It has been said with much justice that " more patients die by the catheter than by the prostatectomy " [10], and it is therefore right that the catheter should have become the crux of surgical inquiry and dispute McEACHERN and his colleagues [11] at the Royal Adelaide Hospital advocate urethral catheterisation After decompression the catheter is tied in In cases of acute retention operation follows decompression at any convenient time within thirty-six hours, " a faster tempo than this is considered to be unsound practice, because there are too many important associated conditions which may be missed if the journey from receiving room to theatre is too short " Chronic retention is relieved by slow decompression, and if the blood-urea-nitrogen is over 40 mg per 100 ml —especially if this is manifest by uræmic symptoms—catheter drainage is continued under chemotherapeutic cover for seven to ten days McEACHERN claims that the dividends of this policy, both in lessened mortality and in shortened convalescence, have been gratifying, and statistical support for this claim is not wanting On the other hand, surgeons who prefer the suprapubic route of decompression, and those who reject any form of catheterisation as an unnecessary evil, can point to results which are at least equally good [12,13] and many would regard McEACHERN's management of chronic retention as retrograde " Slow decompression," WELLS [14] said recently, " a sine-qua-non of recent days, is now, I presume, defunct It was based upon the theory that rapid decompression caused hæmorrhage and suppression of urine, complications now recognised as due to trauma and infection, or to electrolyte imbalance " WELLS also criticised the facile acceptance of infection as an inevitable concomitant of stasis Autogenous infection of the bladder from the kidneys is certainly rare, and stasis per se does not lead to infection Only when stagnant urine is contaminated by catheter or by cystoscope does it become (and remain) infected With many practical obstacles barring the way to routine immediate prostatectomy, the risk of preliminary drainage may have to be accepted, but it remains a grave risk

Urethral catheterisation can lead to bladder infection in at least three different ways Organisms can be introduced by the catheter itself, and those who see this as the main danger prefer the indwelling catheter to repeated catheterisation Others picture the formation of a thin film of " culture-medium " between the catheter and the urethral wall—a broad highway rather than a free passage for organisms—and they recommend withdrawal of the catheter as soon as the bladder has been emptied Finally, the importance of intraluminal spread is shown by the reduced incidence of postoperative infection with the aseptic closed-bladder drainage [15,16] The provenance of the organisms is equally obscure Autogenous sources—the bowel and the traumatised prostatic bed—may account for some infections, but more and more evidence favours true cross-infection.[17]

Unfortunately, catheterisation is still undertaken for no good reason far too often Acute retention can often be relieved by more homely and less dangerous methods, and to pass a catheter merely to measure exactly the amount of residual urine is the essence of meddlesome surgery

Abuse of antibiotic cover is so common that it would be surprising if this branch of surgery were exempt, the increasing proportion of resistant strains of *Escherichia coli* and *Staphylococcus aureus* isolated from specimens of urine after catheterisation need cause no surprise

In their operative technique McEACHERN and his colleagues differ little from surgeons in this country They approach the prostate by MILLIN's retropubic route [18] and follow HARRIS's method in the enucleation of the gland Like others, they have found chemotherapy no substitute for ligation of the vasa deferentia A rise in the incidence of osteitis pubis cast a cloud over the early history of MILLIN's operation, but McEACHERN

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[1] Freyer P J *Brit med J* 1901 ii 125
[2] McGill A F *ibid* 1899, ii 863
[3] Belfield W T *Amer J med Sci* 1890, 100, 439
[4] Fuller E J *J cut gen urin Dis* 1895, 13 229
[5] Morison R Surgical Contributions London, 1907
[6] Thomson-Walker J W *Trans med Soc Lond* 1930, 53, 143
[7] Judd, E S *Coll Pap Mayo Clin* 1917, 9 254
[8] Young H *J Amer med Ass* 1903 41 999
[9] Harris, S H *Brit J Surg* 1934 21, 434
[10] Creevy, C D cited by Wells C A *J R Coll Surg Edinb* 1956, 2, 120
[11] McEachern, A C *Ann R Coll Surg Engl* 1958, 22, 151
[12] Wells, C Prostatectomy Edinburgh 1952
[13] See *Lancet* 1956 ii 343
[14] Wells, C *J R Coll Surg Edinb* 1957, 2, 120
[15] Pyrah, L N, Goldie, W, Parsons, F M, Raper, F P *Lancet*, 1955, ii 314
[16] Goldie, W *Proc R Soc Med* 1956, 49, 1047
[17] Gillespie, W A *ibid* p 1045
[18] Millin, T Retropubic Urinary Surgery Edinburgh, 1947

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have no useful advice to offer the considerable number of people who do not take their troubles to a doctor but whose way of living, if uncorrected, is sure to lead to one of the breakdowns of middle life? To such questions the answer is that sometimes, undoubtedly, the periodic examination can have good results, but that its advantages are very easily exaggerated. Contrary to what is often supposed, the approach of few disorders can be detected before symptoms appear: pneumonia, poliomyelitis, appendicitis, vascular thrombosis, and many other common illnesses strike down people in apparently perfect health. Secondly, early diagnosis does not, unfortunately, by any means certainly lead to successful cure. And thirdly, in many chronic disorders early diagnosis is not particularly important, because they can be cured equally well in the later, symptomatic stage.

The periodic overhaul has a strong appeal to a generation which thinks in terms of machines. But the human body is not a machine, and British doctors may be wise in rejecting this analogy and trying to weigh the advantages against the disadvantages—in practice not in theory. One practical disadvantage is that the cost of adding periodic examination to the amenities of the National Health Service would be enormous. In Soviet Russia a great many doctors now spend a great deal of time on examination of the healthy, and Sir JOHN CONYBEARE's [29] estimate of an extra £100 million a year for such examination is certainly not too high, if it is to be done properly. Could not this money, and the resources it implies, be used by the N.H.S. more effectively in other ways? Another and more fundamental disadvantage is that the system must, for many people, mean more thoughts about illness and more anxiety. Usually the examination itself, when the time came, would relieve such anxiety, and no doubt the majority would take their overhaul unemotionally as a matter of course. But routine checks have their psychological dangers even for the least neurotic. When a minor abnormality is found, and further tests and investigations are necessary to establish its cause, some concern is bound to be felt, and this may leave its mark even when the abnormality is finally found to be of no consequence.

If, then, periodic examination of everybody is very far from being the ideal preventive measure that it may appear, is there anything to be said for a routine health check on particular groups, as proposed by the B.B.C.? Not, we think, very much when it is only an occasional examination by a doctor who knows little or nothing of the examinee. But it may have some value in the special circumstance where a large firm or organisation employs a full-time doctor who will examine key employees at fairly short intervals, and who may be expected to know a good deal about their health and personality. As Dr R. F. GILLMER pointed out,[30] such knowledge will sometimes enable the doctor to detect early signs of physical or mental overstrain, and his detailed records may show significant changes over a period. (A good general practitioner in a reasonably small single-handed practice is in a similar position, and a system of regular examinations may help him in the management of his patients.) The B.B.C.'s scheme may therefore have some usefulness if the Corporation propose to retain one particular doctor's services, and if he is to see each senior employee at least once a year. It would cost them less if they dropped the routine electrocardiography and X-ray examination. The latter is already offered by the mass-radiography service, and in any case the worth of the examination depends on the doctor's alertness. There is a story told of a well-known contemporary American physician who was asked to see an important but ageing business man whose firm proposed to send him on a vital mission abroad. The firm had had an exhaustive series of medical tests carried out, all of which the man passed successfully. Nevertheless, the physician's advice, given after a short physical examination, was uncompromising: "Don't send him." The firm, somewhat taken aback, protested that all the tests had been satisfactory, and asked what had been missed. Back came the reply: "Egg on his waistcoat."

Annotations

HOSPITAL MEDICAL STAFFS

LAST week the Minister of Health announced agreement with the Joint Consultants Committee to set up a joint working party "to study, in the light of experience of the hospital service since 1948 and of all other relevant considerations, the principles on which the medical staffing structure in the hospital service should be organised."[1]

This is welcome news. The working party's task will presumably include a review, in some form, of consultant needs—a review which the profession's representatives have repeatedly called for, and in which attention will no doubt be given to the unequal distribution of consultants[2] and to consultant work now done by others. But the working party will be concerned with larger issues. In particular it will want to discover whether, under the existing system, peripheral hospitals can continue to secure enough medical staff below consultant level. The number of registrars is fixed by other factors than the convenience of the hospital, and there is no inherent reason why this number should suffice for all demands; indeed there are increasing indications that it does not suffice. For instance, last month Luton and Hitchin Hospital Management Committee, impressed by the difficulty of filling the two registrarships in anæsthesia at Luton and Dunstable Hospital, decided to seek permission to regrade one post as that of S.H.M.O. The committee was informed that there are some registrars who, though unlikely to obtain the highest qualifications and become consultants, are nevertheless competent anæsthetists and valuable members of hospital staffs.[3]

We ourselves know of no sound evidence that the existing medical-staff structure, with the long leap from senior registrarship to a consultant post, has favoured efficiency in the hospital service, and it has even operated

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29. *ibid* Feb 22, 1958.
30. *ibid* Feb 21, 1958.

1. See *Lancet*, April 26, 1958, p. 906.
2. *ibid* April 5, 1958, p. 748; Joules, H. *ibid* p. 739.
3. *Luton News*, April 17, 1958.

agrees with MORTENSEN[19] that this complication is far less common today[20] Bleeding, on the other hand, is certainly heavier when the prostate is approached by the retropubic than by the transvesical route[21 22], and "inspection of the sucker bottle and the swabs at the end of each operation will justify the routine administration of 600 cc of blood in all cases"[11]

If minor differences in operative technique are unlikely to arouse much controversy, the same may not be true of postoperative management In addition to ADAMS's[23] "third ureter"—a ureteric catheter introduced either suprapubically or alongside the urethral catheter—MCEACHERN administers for the first twelve to twenty-four hours after operation an intravenous drip, somewhat fancifully referred to as the "fourth ureter"

Few will dispute that the parenteral administration of fluids has many advantages over "pressing fluids" by mouth, but that "the third ureter compensates for, while the fourth ureter overcomes, Nature's postoperative oliguria"[11] is only true if these terms are interpreted so widely as to lose all meaning "Nature's postoperative oliguria" is part of the body's complex response to any form of trauma, and far from being amenable to correction by intravenous fluids, it is likely to be aggravated by it The "third ureter" does correct postoperative oliguria in the sense that it contributes a flushing system while there is danger of bleeding and of catheter blockage But the "fourth ureter" does nothing to overcome it What it does do is to correct the very reverse—namely, the excessive loss of water and electrolytes which may follow relief of long-standing obstruction

Patients with chronic urinary obstruction tend to accumulate a backlog of salt and crystalloids, shown in part by œdema, a high blood-urea-nitrogen, and a total plasma osmolarity higher than the sum of measurable anions and cations Some desalting and hæmoconcentration may result from vomiting and from pulmonary water loss, but the "dehydrated" appearance of these patients is usually due to uræmia, and they are, in fact, grossly waterlogged As soon as obstruction is relieved—whether by simple catheterisation or by prostatectomy—solute diuresis begins If renal function is normal this is a transient phase, the renal tubular cells quickly regain their ability to process the filtrate and to concentrate the urine, and dehydration and desalting remain minimal In older patients, however, some tubular damage is common, and the postobstructive diuresis may result in severe salt and water depletion, hæmoconcentration, and decrease in plasma-volume[24] In addition, there is a tendency to acidosis, suggesting impairment of the enzyme systems in the proximal tubules[24] 5–8 litres of urine of fixed specific gravity may be passed in twenty-four hours, and the sodium loss may be massive (Largely according to the water balance, this may lead to a significant fall in the plasma as well as the total sodium concentration)

The guiding principle of intravenous-fluid therapy after prostatectomy should be to preserve the precarious postobstructive fluid balance rather than to maintain a steady stream down the ureters MOORE[24] believes that "this is one of the few situations in surgery where a conscientious attempt should be made each day to repair the urinary loss of sodium salts", and large infusions of sodium bicarbonate or lactate may be required This is no easy task, especially postoperatively, and clinical judgment must temper biochemical considerations (In the presence of pitting œdema, or of other evidence of increased total body sodium, it may be wise, for instance, to allow the sodium drain to proceed for a few days before any attempt is made to repair the loss)

Most surgeons will agree with MCEACHERN that the indwelling catheter is "the pivot on which the whole technique of modern postoperative management depends", and that "there is no aspect of surgery in which trained and experienced nursing is more necessary"[11 20] There is, on the other hand, much to be said for not laying down a definite time after which the catheter should be removed The correct time is neither two days nor two weeks after the operation, but whenever the patient can empty his bladder unaided and completely A late postoperative complication which has caused some concern at the Royal Adelaide Hospital is postmeatal stricture Its frequency seems to be increasing, but its causes remain obscure MCEACHERN suggests that several factors may have to be considered: the size of the catheter in relation to the calibre of the urethra, the duration of catheter drainage, chemical irritation by certain types of red rubber,[25] and altered tissue response to infection as a result of chemotherapy[26] Fortunately this complication is of importance only when neglected, and in only 2 patients of the Adelaide series was repeated dilatation necessary

Routine Medical Examinations

THE practice of visiting a doctor or clinic regularly for a routine "health check" has long been common among the wealthier citizens of the United States, and there are signs of its increase in this country The value of such examinations, which may include radiography, electrocardiography, and laboratory tests, has lately been the subject of correspondence in *The Times* When Captain L P S ORR, M P,[27] asked whether it is proper for the British Broadcasting Corporation to spend public funds on private routine examinations for its senior executives, the B B C chairman[28] replied that £900 a year is "a small premium to pay towards the maintenance of the health of trained senior staff" Whereupon several distinguished physicians declared that routine examinations of this kind are virtually useless for their intended purpose—namely, the detection and successful treatment of symptomless disease

Some readers of *The Times* will have discounted these medical utterances on the ground that doctors in general are commonly more interested in treatment than prevention Such critics can point not only to America but also to Soviet Russia, where periodic examinations are officially regarded as a most desirable development in medicine, because they bring disease to notice at an earlier and more readily treatable stage Is it not a fact (they may say) that many patients suppress and conceal serious symptoms which a routine examination would soon elicit? Would the profession avascular necrosis is inevitable) In these cases it is important not to discard clinical judgement, and the surgeon who examines his own radiograph is more likely to spot the minor lesions Among the most difficult of these to discover is the small stress fracture, and Burrows[8] has emphasised that many views of the tibia may be necessary to demonstrate the small area of stress infraction In many cases we undoubtedly lay too much stress on the slight lesion of the bone and forget or ignore the extensive soft-tissue destruction with which this may be associated

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[19] Mortensen, H *Proc Urol Soc Aust* 1950, 4, 43
[20] See *Lancet*, 1956, i 328
[21] Goldstein, A E, Rubin S W *J Urol* 1948 60 743
[22] Goodyear, W E, Beard, D E *ibid* 1949, 62, 849
[23] Adams A *Ann R Coll Surg Engl* 1951, 8, 279
[24] Moore, F D *New Engl J Med* 1958 ,258, 377
[25] Handfield-Jones R P C, Lewis H B M *Lancet*, 1952, i, 585
[26] Kirkland, K *Med J Aust* 1955, 2, 921
[27] *Times*, Feb 5, 1958
[28] Fforde, A *ibid* Feb 6, 1958

INFANTILE SCURVY IN CANADA

THE incidence of scurvy in infants has shown a decided rise in Toronto in recent years, and Whelen et al[9] have described the clinical findings, feeding histories, and errors in diagnosis in 79 cases treated in the wards of the Hospital for Sick Children, Toronto, in the five-year period 1951–55 Until 1953 the average yearly total of admissions for scurvy over a period of twenty-six years had only been 7, whereas in 1954 it was 46 Half of these patients lived in Toronto The age at onset of symptoms and the clinical manifestations were typical and call for no special comment What is surprising is that in this age of vitamin-consciousness the disease should show a striking rise in incidence (which is apparently also evident in Winnipeg) in a city with a good record for pædiatric services and public health

The cause was clear Nearly four-fifths of the infants had not received either suitable fruit juices or synthetic ascorbic acid for six weeks before admission In two-fifths some orange juice had been offered in the early months but had not been persisted with The average duration of breast-feeding in the series was less than 11 days, and the alternatives as regards milk—evaporated or pasteurised liquid milk—did not contain enough vitamin C The infants in the hospital invariably improved rapidly when given therapeutic doses of vitamin C, and this was held to discount the statement of parents in a fifth of the series that their children had been given enough of the vitamin in their diet The next question was whether in these instances, or in any of the series, " the well-meaning but unnecessary manipulations of the most imaginative mother " had destroyed the vitamin C in any of the fruit juices used Surprisingly, in view of the general impression that heat will destroy vitamin C, the Toronto workers found that the addition of boiling water, boiling the orange juice, alkalinisation, and alkalinisation followed by boiling, applied to fresh, tinned, or reconstituted frozen concentrated orange juice, did not reduce the vitamin-C content to a dangerously low level Even boiling for forty minutes " in an uncovered, chipped, rusty, enamelled saucepan " reduced by only 15–25 5% the vitamin C measured by decolorisation of the accepted phenolindophenol dye solution

These results are important in view of the alarm expressed by Moncrieff[10] at the use of the pasteurised orange juice now supplied by certain milk firms for babies and young children The plain fact seems to be that babies get scurvy because they do not receive orange juice at all One reason is thought to be the unnecessary use of synthetic multiple-vitamin preparations which may not, in fact, contain any vitamin C One of the suggestions made by Whelen et al is that vitamin C might be incorporated into certain foodstuffs commonly consumed by infants, as is done with vitamin D in evaporated milk Every infant requires at least 30 mg of vitamin C daily, and this, it is suggested, should be emphasised more strongly by doctors and others concerned with the supervision of infant feeding

OVERSEAS STUDENTS AND POSTGRADUATE STUDY

ORGANISERS of postgraduate medical education in this country have no easy task their sails have to be trimmed to many winds The clinical requirements in Great Britain are a world away from those in remote tropical or deprived communities, and these, again, differ from the demands of our wealthy and energetic Dominions In the great days of British rule overseas, students automatically turned to Britain for training in our views and methods Of late years some things have changed, but tradition and prestige, and perhaps proved value, still ensure a flow of men and women from all parts it is often said, too, in poorer countries that there is more of relevance to be learnt from our financially restricted health-service system than from affluent and uncontrolled American methods It is an honour to us that they come, though we should not assume it is purely a love of Britain and of knowledge that brings them the coveted diploma often means everything Obviously we as a nation benefit from these contacts on many fronts other than the purely scientific, and we should ask ourselves from time to time whether we are giving these friends from abroad what they need, and whether we are giving it to them well enough

Dr Cicely Williams, writing in this issue and the last on child welfare, clearly thinks that we are not Her penetrating remarks are derived from observations in South East Asia and Africa She says with reason that a study of rare disorders in the Western setting of large institutions is not much help (and may even be a hindrance) to the doctor from a far-off land Though Dr Williams may take an over-rosy view of the potential sociological importance of doctors, it could be said that others besides our overseas colleagues would benefit from greater understanding of social factors (for example, in smoking and dietary fat) If we feel that our foreign contacts are worth encouraging (and surely they are) perhaps we should readjust our emphasis Clearly it is out of proportion for an Asian to be examined in detail on the Klippel-Feil syndrome and not on kala azar, similarly it is unnecessary for the provincial specialist here to be acquainted with recent trends in leprology There seems to be room for some curricular adjustment, and there might be advantages in an alternative second paper in some of our specialist diplomas, dealing with tropical, nutritional, social, and public-health questions It would tax the resources of our teachers, for, while many have had tropical experience in the Armed Services, this does not help much in the understanding of village life and problems Short visits to these countries do not help much either, since, as Dr Williams points out, it is not easy for the European specialist to see beyond the shiny new prestige institutions to the neglected aspects of medical and social life Even a doctor in daily contact with Indian rural patients may be amazed at his ignorance of their everyday beliefs and superstitions, lately described by Carstairs[1] against some of the staff themselves—notably those senior registrars who have failed to make the leap, and senior hospital medical officers who have been largely excluded from the competition In the short run, insistence that (with stated exceptions) permanent medical staff shall be grouped together as consultants has favoured those of them who, relatively, apply less skill or carry less responsibility than some of their colleagues In the long run this grouping may tend to operate against those with relatively higher skill or a heavier responsibility We have more than once expressed the belief that both the hospital service and the profession would have cause to welcome the abolition of the SHMO grade and the creation of a new one—that of specialist—to include all on the road to a consultant post besides some who aspire to go no further[4] Not all our readers subscribe to this view[5] But both those who do and those who do not will look with relief to the working party as a medium for discovering facts that may open a way out of the present damaging impasse

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[8] Burrows H J *J Bone Jt Surg* 1956 38B, 83

[9] Whelen W S Fraser D , Robertson, E C , Tomczak, H *Canad med Ass J* 1958 78 177

[10] Moncrieff A *Lancet*, 1957 ii 340

[1] Carstairs, G M The Twice-Born London, 1957

The help meanwhile proposed by the Minister for some time-expired registrars[1] takes a devious and obscure form, but the Minister's hands are partly tied by the Royal Commission on Remuneration and by the Government's avowed determination to avert a general increase in salaries and wages We see no reason to doubt the sincerity of his assurance that the new posts for selected senior registrars, with security of tenure and a somewhat higher salary, are to be provided " pending and without prejudice to the working party's report " and " are not to be regarded as a substitute for additional consultant posts " Certainly, we should not wish to see the present first-aid measure cited as a precedent for setting up an intermediate grade If (as we hope) such a grade is to come it should be introduced deliberately, frankly, and if possible by general consent

MODIFIED ASPIRIN

ASPIRIN, the wonder drug of the time when it was introduced, is still unsurpassed in its field Idiosyncrasy to it is very rare, but occasionally it causes gastrointestinal hæmorrhage, probably owing to gastric erosions, and less rarely it gives rise to symptoms of gastric irritation The forms, and the prices, of aspirin preparations vary widely Aspirin *B P* gr 5 costs a hospital 9*d* per 100, whereas a proprietary preparation containing aspirin gr 5 with aluminium glycinate and magnesium carbonate costs 6*s* 6*d* plus 1*s* 11½*d* purchase-tax A high price is sometimes put on preparations claimed to be exceptionally pure, but today it is unlikely that impure aspirin is sold, the production of salicylic acid by hydrolysis is prevented by airtight storage

The effectiveness of mixtures of aspirin with other analgesics, such as codeine, depends mainly on their aspirin content, the small amount of codeine, though of little therapeutic value, produces constipation in some patients Calcium or soluble aspirin is about equal in analgesic effect to aspirin, but is often preferred because of its lesser tendency to produce gastric effects Crushing aspirin is perhaps equally efficacious, though less convenient, but a badly made aspirin tablet may disintegrate slowly, and in this respect calcium aspirin is better

Sodium bicarbonate was once prescribed with sodium salicylate to minimise gastric irritation Behind this may have lurked the idea of " acidosis " brought about by salicylism—though, as we now know, salicylate causes overbreathing with subsequent alkalosis Mixing aspirin with a buffer seemed a logical development to the incorporation of bicarbonate with salicylate, and several reports suggested that gastric distress was less common with buffered aspirin than with ordinary aspirin[1–4] But studies conducted by blind random selection techniques have failed to show any difference between the two forms[5, 6], and blood-salicylate curves were found to be the same (Batterman[5] showed that the incorporation of bicarbonate 1 2 g with aspirin 0 6 g lowered the free and total plasma-salicylate levels, thus confirming an earlier assumption) Further tests on buffered and simple aspirin are needed in order to establish beyond doubt their value in relation to each other

OCCULT FRACTURES

DIAGNOSIS of the fracture that is suspected clinically but cannot be demonstrated radiographically is an important orthopædic problem It arises most commonly in the wrist, a fracture of the carpal scaphoid may not be apparent on the radiograph until several weeks after it has been sustained Waiting for radiographic evidence in these patients may invite delay in union and ischæmic changes in the proximal fragment of the bone, yet it is scarcely more satisfactory to immobilise in plaster all patients with the clinical signs of a scaphoid fracture, since many will resolve without a fracture ever becoming visible

In children spiral fractures of long bones commonly do not show on the early radiographs, and very often confirmation of a clinical diagnosis depends on the later X rays Sometimes the only change which ever becomes apparent is periosteal thickening, but more commonly the fracture is seen some two or three weeks after the injury Fractures near the epiphyses of long bones may also be difficult to display, but in this region immobilisation is less important In the upper limb of the adult minor fractures of the neck of the radius or chip fractures of the head of the radius may become apparent only after repeated radiographs have been taken, and special views in many positions may be necessary In the hip the undisplaced fracture of the neck of the femur is still occasionally misdiagnosed Many of these patients will recover full function without any relief from weight-bearing, but in others the diagnostic failure results in non-union or avascular necrosis of the head of the femur Fractures of the spine may be missed because the radiographs show little or no deformity, but this error in diagnosis is often of little importance since slight injuries to the vertebral body can well be treated by early exercises and mobilisation

Reich and Rosenberg[7] emphasise the importance of relating the clinical to the radiological signs They define the occult fracture as one which gives clinical signs of its presence but cannot be demonstrated by X-ray examination until reparative changes have occurred (Perhaps this is an over-optimistic definition since some of the fractures may not be diagnosed until delay in union or

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[4] *Lancet* 1957 i, 1127, 1133 1957, ii 1099

[5] *ibid* 1957, ii 1174 1227, 1228 1229, 1281 1282, 1336, Jan 4, 1958, p 52 p 53, Jan 18 p 164 Jan 25, p 220, Feb 1, p 261, Feb 22, p 437, March 1, p 481, April 5, p 739

[1] Paul, W D, Dryer, R L, Routh, J I *J Amer pharm Ass* 1950, 39 21

[2] Tebrock, H E *Industr Med* 1951, 20, 480

[3] Freemont-Smith, T *J Amer med Ass* 1955, 158, 386

[4] Feinblatt, T M, Feinblatt, H M Ferguson, E A, Price, A H, Healey, J E Allison, W A *St J Med* 1958, 58, 697

[5] Batterman, R C *New Engl J Med* 1958, 258, 213

[6] Cronk, G A *ibid* p 219

[7] Reich, R S, Rosenberg, N J *J Amer med Ass* 1958, 166, 563

Special Articles

FAST AND SLOW STREAM MEDICAL WARDS

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JUST as road travel is improved by the provision of fast and slow lanes, so the diagnosis and treatment of medical patients could be made more efficient by the care of patients in wards with a fast or a slow rate of turnover of beds.

In the past this division has taken place, but between hospitals rather than between wards. The slow-stream wards are concentrated in special hospitals for the chronic and elderly sick. Anyone who has worked in such a hospital knows, however, that many of the patients admitted are in need of just the same diagnostic skills and treatment as the patients who happen to be admitted to a general hospital. Often it is the availability of beds at the time of a request for emergency admission that determines whether a patient of 60–65 is admitted to a geriatric hospital or to the wards of a general hospital; this is tantamount to saying that the decision is largely one of chance. If the patient admitted to a geriatric unit is found to require investigation or treatment which cannot be provided at that hospital, he must be transferred to a general hospital. If, on the other hand, it is found that the patient admitted to a general hospital is unlikely to get well within three to six months, it may be desirable to transfer him to a geriatric hospital. Such transfers are difficult to achieve unless the physician-in-charge has beds at both hospitals, and in any case they are administratively wasteful and emotionally damaging to the patient.

One may hear physicians and surgeons who work in a hospital where the weekly cost of an occupied bed is £25 or more complain because they cannot easily transfer their more chronic patients to a geriatric hospital, and on the same day listen to the grumbles of geriatricians who find themselves dealing with certain inpatients for whom they have inadequate facilities for investigation and treatment. I repudiate the suggestion that all elderly sick patients need full investigatory facilities. The clinical senses are usually quite sufficient to reach an accurate diagnosis and prognosis, but there are some cases where careful investigation is necessary and useful.

The problem is more one of the slow recovery and of social difficulties to be overcome before the patient is discharged. This sort of patient can be inexpensive to nurse and to treat, but he needs a hospital bed for longer than a young patient admitted for—shall we say—stabilisation of his diabetes. The overall cost of his treatment may be much the same as that of the younger patient who in his shorter stay uses up more of the time of highly trained, highly paid staff, and makes fuller use of expensive diagnostic facilities.

Therefore we have on the one hand a need for acute wards, fully staffed by highly skilled personnel, in which the turnover is so rapid that 30 patients per annum can be treated per bed. On the other hand there is need for slow-stream wards staffed by the same medical team, but with a different grade of nurses, where the need for investigation is less, and the emphasis on nutrition, rehabilitation, and nursing care is greater.

Acute wards usually contain 25% of ambulant patients admitted for special investigations, 25% acutely ill and requiring hour-to-hour treatment or intravenous therapy, and the remainder recovering from acute illness or being treated in bed. The slow-stream wards usually contain 20% bedfast patients with dementia or various forms of paralysis, 20% of patients who are likely to die within six months from carcinoma or other fatal diseases, 20% frail ambulant patients who are unable for social reasons to maintain a reasonable life outside a hospital, and the remaining 40% elderly but capable of recovery, given time and patient effort—cases of congestive heart-failure, hemiplegia, and chronic lung disease. In such wards it should be possible to treat 4 patients per bed per year.

The present trend towards the development of geriatric and exclusively acute general hospitals leads to an inequitable distribution of nursing staff. The geriatric hospitals have the greatest difficulty in recruiting staff in spite of State enrolled assistant nurses scheme, and the free use of nursing auxiliaries. The teaching hospitals have nurses to spare (though this would rarely be admitted), and these nurses sometimes have little experience of the nursing of the elderly sick. This is a pity because in the next twenty years we must face a 14% increase in the numbers of elderly sick. It is fortunate that many elderly patients are in fact nursed and treated in acute general hospitals today, but it is nevertheless a pity that nurses in training see little of the intensive methods of rehabilitation and perhaps do not experience the different mental approach needed in the care of the elderly sick.

THE OBSTACLES

One of the main obstacles to the integration of acute and geriatric medicine in hospitals is the policy of the General Nursing Council, which makes it difficult to house training schools for State-registered nurses, and State enrolled assistant nurses in the same hospital. Nurses under S.E.A.N. training may not work in the same wards as nurses under S.R.N. training. At the time ten years ago when it was clear that many hospitals would have to close down unless a shorter course of nurse-training could be provided, the State enrolled assistant nurses scheme was born of necessity. After this lapse of time, it must be clear that the standards of nursing have not suffered by the introduction of the State enrolled assistant nurses scheme, and State-registered nurses have not contracted any dread diseases from working in close proximity to State enrolled assistant nurses.

Another obstacle to the inclusion of slow-stream wards in acute hospitals is the system of classification of hospital by the Ministry of Health into, "acute", "mainly acute", &c.—each with its own scale of finance. This makes the hospital management committees, which are jealous of the status of their hospital and anxious for the fullest financial provision, unwilling to admit more than a very small proportion of elderly sick patients, and certainly unwilling to segregate them in special wards.

A third difficulty is the attitude of the medical profession. Those working exclusively in acute hospitals may see themselves as a superior breed who should not be troubled by the problems of those patients who obstinately refuse to get better within a month, or they may be interested mainly in their specialty. Whatever the reason, there is resistance to the incorporation of geriatric services into an acute hospital, which seems hardly justified when the complaint is so often heard that such and such a "chronic hospital" will not take

If, however, the training and diplomas we have to offer are not (through other eyes) all they might be, it is also sadly true that foreign students arriving here are sometimes inadequately prepared for them Linguistic and academic difficulties added to those of everyday adaptation may plunge a young doctor out of his depth, and he may never really resurface Something more could be done from both ends by way of selection and preparation, although some Governments and the British Council already do valuable work We believe that if Britain (and especially London) is to remain a sought-after centre of teaching and research it must broaden its horizons Dr Williams has told us something of what is needed from the pædiatricians her words are wise and deserve careful study

NARROWED ATTENTION

STRONG emotion, acute stress, or the action of certain drugs can dramatically reduce awareness of the immediate environment Callaway and Dembo [1] discuss the possible neurophysiological basis for this familiar phenomenon, for which they suggest the term "narrowed attention", and which, in their view, is something other than altered ability to sense or respond to a stimulus It is, they believe, rather a change in the process which determines to what extent behaviour shall be influenced, at a given time, by each possible source of stimuli The more a person's attention is "narrowed", the less will his behaviour be influenced by factors peripheral (in time or space) to the focus of attention

Callaway and Dembo believe that "narrowed attention" augments internal sources of motivation, that it is associated with (but is not the result of) central sympathomimetic activity, and that both phenomena are perhaps secondary to stimulation of the brain-stem reticular formation To establish the correlation between "narrowed attention" and central sympathomimetic activity, they observed the effect on their subjects' behaviour of sympathomimetic drugs They report that amyl nitrite, adrenaline, and methamphetamine produced changes in size-matching, nerve-gases, amyl nitrite, and methamphetamine produced changes in muscle response to loud sounds, and methamphetamine produced changes in galvanic skin response and in guessing behaviour All the changes were indicative of "narrowed attention"

Calloway and Dembo remind us of the everyday instances of narrowed attention people may become "blind with rage", or the football player ignore his injured hand in the heat of the game, and they quote Kinsey's [2] finding that orgasm narrows attention, and Shipman's [3] that children, waiting at the dentist's, recall fewer details of their surroundings than do controls Callaway and Dembo mention two instances in which, during their experiments, subjects showed "narrowed attention" apart from their experimental responses One student with a broken arm in a cast felt less uncomfortably aware of it under methamphetamine The same drug led another student to be blind to the polite rebuffs he encountered while trying to "date" a female technician, and to desist only when faced with a flat refusal From the clinical viewpoint, they suggest that the action of methamphetamine in improving the behaviour of hyperkinetic children, described by Laufer et al [4] as "unusually sensitive to stimuli flooding in from both peripheral receptors and viscera", may be related to the narrowing of attention produced by the drug

This study will encourage other approaches to the problem of the relation between sensory stimuli and internal processes

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1 Callaway, E Dembo, D *Arch Neurol Psychiat* 1958, 79, 74
2 Kinsey, A B, *Pomeroy*, W B, Martin C E, Gebhard P H Sexual Behaviour in the Human Female, p 613 Philadelphia 1953
3 Shipman V M A Thesis presented to the Eastern Psychological Association 1955
4 Laufer, M W, Denhoff, E, Solomons, G *Psychosom Med* 1957, 18, 38

MENTAL ILLNESS AND SOCIAL CLASS

THERE has been an increasing trend in medicine lately for the searchlight to be turned, as it were, inwards towards us, the doctors On an organic level we all know of the survey into our smoking habits, and we should be glad indeed to find out why we seem so liable to coronary-artery disease The psychoanalysts take the investigation of the doctor further than others, insisting that the aspiring therapist undergo a long and difficult training analysis that will give him insight into his own mental mechanisms Merton [1] recently summarised some of the sociological work done in medical schools in the United States, and there have been studies of mental hospitals and their personnel [2 3] The permeation of anthropological and sociological influence is particularly seen in investigations of mental illness, though the fusion of specialties is by no means always friction-free [4] The United States is clearly far ahead of us in this type of project

On April 17 Prof A B Hollingshead, the distinguished sociologist from Yale University, outlined at the Maudsley Hospital some of his work with Dr F C Redlich,[5] on mental illness and social class, especially that related to the practice of different psychiatrists and psychiatric institutions He studied all those resident in New Haven (Connecticut) who, during six months in 1950, had undergone psychiatric treatment, wherever that treatment had been given He graded the 1900-odd cases according to his 5-scale social-class system [6] and correlated this with the type, place, and duration of therapy Some expectations were confirmed—for example, that psychoanalysis was almost exclusive to the richer classes, whereas the poorer made do with simple and brief measures For the psychoses he showed that the wealthier patients received earlier treatment and were discharged from hospital more quickly, but that they were readmitted more frequently A more surprising finding was that therapy correlated little with diagnosis, and that the type of treatment was therefore more or less determined before the patient ever met the doctor he had selected Professor Hollingshead noted the division between those psychiatrists who used physical treatments and those who eschewed them and concentrated exclusively on psychological methods and interpretations The two schools are certainly to be found in this country,[7] but here, apparently, the boundaries are less clear-cut

It seems, therefore, that just as a person's class position determines his place of residence, friends and hobbies, so it decides—anyhow in the United States—the therapy he will receive when mentally ill Perhaps Professor Hollingshead will one day tell us to what extent it determines the type of illness he will get A similar piece of research in this country would not be easy, but might be rewarding, and a survey of the views and methods of all psychiatrists within six miles of St Pancras would be worth attempting

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1 Merton, R K, Bloom, S, Rogoff N *J med Educ* 1956, 31, 552
2 Stanton A H, Schwartz, M S The Mental Hospital London, 1954
3 Greenblatt M, Levinson, D J Williams R H *The Patient in the* Mental Hospital Chicago, 1957
4 Simmons O G, Davis, J A *Amer J Sociol* 1957, 63, 297
5 Hollingshead, A B Redlich F C Social Class and Mental Illness New York 1958 (To be published in London in July)
6 Hollingshead A B Elmtown's Youth London, 1949
7 Cobbleigh, R *Lancet*, Feb 8, 1958, p 310

centuries, but now, by newspaper articles and advertisements, it has been made into a respectable symptom

If there is any real increase in tension it may well be the result of tranquillisers, because their withdrawal encourages the symptom to develop

Irritability is another symptom often treated by sedation. Caution is particularly necessary here because irritability may so easily be a manifestation of physical illness—thyrotoxicosis or peptic ulcer—and sedation may mask the underlying disease

PHARMACOLOGICAL SEDATION

Two groups of drugs are used in sedation—hypnotics and tranquillisers

Hypnotics are liable to produce a befuddled kind of sedation, and have the further disadvantage that psychoneurotics may save them up for half-hearted suicidal attempts Moreover, people weak in character may become addicts

Tranquillisers belong to four main groups

The rauwolfia group
The chlorpromazine group
The benzhydrol group—azacyclonol, benactyzine, and others
The muscular relaxants related to mephenesin, of which meprobamate is the most widely known, the most widely swallowed, and perhaps the most expensive of all the tranquillisers

Each group has good points and disadvantages The rauwolfia group may calm grossly disturbed psychotics but sometimes produces severe depression. The chlorpromazine group achieves dramatic results in some psychotics with gross excitement or tension, but has many side-effects including obstructive jaundice The benzhydrol group are specific in combating the madness produced by the administration of lysergic acid or mescaline, but the treatment here should be to withhold these drugs rather than to neutralise their effects Otherwise the benzhydrol group, on controlled testing, have shown little outstanding value The last group, the muscular relaxant meprobramate compounds, have become the rage in America. Their tendency to produce addiction to larger and larger doses and their high cost (over twenty times that of amylobarbitone) mean that much caution must be used in prescribing them

Every sedative drug has imperfections, and the search for the perfect one will continue—" since ", as Aldous Huxley remarks, " reality, however Utopian, is something from which people feel the need of taking pretty frequent holidays "

OTHER MEANS OF SEDATION

But sedation is not by pharmacy alone There are the social sedatives, tobacco and alcohol, which give rise to much pleasure but also much illness There are physical means of sedation—massage, warmth, and appropriate sights and sounds, particularly those of a monotonous or repetitive kind (I have observed that housewives appear to achieve a kind of group sedative ecstasy when seated in rows watching their laundry gyrating interminably behind the portholes of a washing-machine) For many people activity is the best sedative, and Kipling prescribed it for that common psychoneurosis—the hump The sedative effect of music is well known to mothers singing their babies to sleep with a lullaby, and an interesting example of the use of sound in sedation is that of Sir Despard Murgatroyd in *Ruddigore*, who tranquillised his wife, whenever she was getting out of hand, by merely saying " Basingstoke, Basingstoke, my dear ’

Nevertheless, though sedation can be achieved with the use of drugs, heat, sight, or sound, it is more logical to quieten a mind directly than by stupefying its physical casing Despair is best treated with hope, not dope Psychotherapy is the basis of all sedation and the use of drugs must be subservient to it—a temporary measure to tide a patient through a critical phase, not a permanent requirement like insulin for diabetes The technique of such psychotherapy is not easily taught. The secret of it is the art of listening—allowing disturbed patients to unburden their load of tribulations Even though most of the burden has to be shouldered again after the interview, it is easier to bear if somebody else has seen how heavy it is A problem is easier to countenance if it has been aired and put into words I felt rather small recently when a father, thanking me for giving some psychological treatment to his son, said " I think it's done him a lot of good being able to tell all his troubles to someone. When I was his age, I used to tell all my troubles to a large rubber duck, and it seemed a great help I suppose you're much the same sort of thing " I had not previously considered myself as the therapeutic equivalent of a large rubber duck, and found it both humbling and enlightening

Yet sedative psychotherapy is not achieved solely by listening The doctor, however effective a rubber duck he may be, has to emit an occasional quack Talking to patients or to their relations is an art that cannot be taught. Only experience and instinct will give a doctor the knowledge of when to probe and when to leave alone when to chide and when to reassure, when to speak and when to remain silent.

STIMULATION AND SEDATION

Most of what I have said about sedation applies again to stimulation. Stimulation can be achieved by drugs (ephedrines, amphetamines, and others), by social stimulants (tea and coffee), by physical means (cold baths), and finally by psychological means (stimulating music, stimulating conversation, and, very rarely, stimulating lectures or speeches)

One man's stimulus is another man's sedative, and the strictures that I mentioned earlier about sedatives apply to pharmacological stimulants They too should be used only to tide a patient through a critical phase, not a permanent requirement like insulin for a diabetic. Today we often find sedatives and stimulants are being prescribed together both too lavishly and for too long

Lately I saw a nervous young woman, who had been attending another hospital for several years She was receiving quinalbarbitone sodium gr 3 twice daily, amylobarbitone sodium gr 6 every night, and two capsules of prolonged-action amphetamine compound daily, together with one and a half hours' group therapy once weekly, and half an hour's individual psychiatric interviews twice a week. She was not any better!

Such extravagance can be expensive, dangerous and unhelpful

Stimulants are necessary to savour the humdrum and to enliven the drab, but they must be used sparingly, over-stimulated senses are less perceptive The palate repeatedly soused with vinegar is less likely to enjoy the flavour of zambaglione

The amount of stimulation available to modern man is increasing and has perhaps reached its apotheosis at Las Vegas, a city wholly dedicated to pleasure, boasting a twenty-four-hour service of every kind of entertainment and refreshment. Beside every hotel bed is a Bible and a free packet of ‘ No-Doze ’ tablets A notice reminds the visitor " If you go to sleep in Las Vegas you are not pulling your weight. You are here to enjoy yourself Help yourself to No-Doze tablets " Another the chronic cases they wish to transfer Surely the solution to this problem is to have the chronic beds under their own care and under the same roof as the acute cases This is, of course, a problem which affects physicians more than it does surgeons, but the surgeons and orthopædic surgeons should be glad to have slow-stream beds in their own hospitals to which they could transfer patients by asking a physician to " see and take over "

Then lastly there is the question of finance Could such a scheme cost more than the present plan of segregation? I think that there would be certain savings in transport, duplication of case-records, and movements of staff Expense might rise owing to the greater use of investigatory and treatment facilities for elderly patients, but this may prove an economy in the long view Provided that we face the fact that the elderly, chronic, or subacute sick need to be nursed and treated in a different type of ward, with a different type of nursing staff, and that the physicians responsible realise that they must look at their patients with the low-power rather than the high-power of their minds' " microscope ", then there is no real reason why expenses should rise Much will depend on the guiding influence of the physician-in-charge, and much will depend on a clear-headed outlook of the hospital management committee It should be accepted, for example, that slow-stream beds could be closer together than acute beds, but day-room facilities are essential, and a few physiotherapeutic tools, such as walking-machines and parallel bars, should be kept close to the slow-stream wards, and not necessarily in the main physiotherapy department

ADVANTAGES

If the integration of slow and fast stream medicine is accepted as a valuable policy for the future, there should be no difficulty in achieving the end, for the means are easily available Already, by the sheer necessities of staff recruitment, the geriatric hospitals are developing acute wards, X-ray departments, and pathological laboratories so that a more interesting type of patient can be admitted and cured It is only in this way that they can hope to recruit nursing and medical staff to care for the slow moving type of case The next necessity is for the acute general hospitals to accept in their planning a provision for slow-stream wards to be run in parallel with their fast-stream wards One medical team of two physicians should be able to staff two fast-stream wards of 30 beds each, and two slow-stream wards of 30–40 beds each, making a block of 120–140 beds

By this scheme it should be possible to make the fast-stream wards really efficient with a high rate of turnover of cases, since any patient likely to block a bed, but no longer needing special facilities such as transfusion, can be transferred to the slow-stream ward where the emphasis is more on rehabilitation and liaison with social-welfare organisations than on the intricacies of modern treatment The same physician should care for the patient throughout, so that he cannot regard the slow-stream ward as a " dump " for his less successful cases but as a place where illness is alleviated or managed as well as it can be All new patients should be admitted first to the fast-stream ward, unless the diagnosis has been fully established before admission and the case is better dealt with in a slow-stream ward

Such a policy of integration is probably acceptable to or accepted by regional hospital boards because they are well aware of the difficulties in recruiting staff to exclusively geriatric hospitals My purpose is to raise the matter at medical level—to show the positive advantages to a physician in having acute and chronic beds under his care, and the improvements in turnover and standards of medical care which could follow from such integration At nursing level, it is most important to appreciate the great differences between the care and treatment necessary for a young woman in an addisonian crisis (where the nurse must possess medical knowledge, skill, and great powers of observation) and the care and treatment of an 80-year-old lady with a hemiplegia, where all the old nursing virtues of good lifting, cleaning, and care and kindness must be brought into play and where often a devoted State enrolled assistant nurse will do better than a clever student nurse Surely it is time to drop the segregation of S R N trainees and S E A N trainees, and to recognise that both grades are necessary, useful, and capable of mixing together without harm to their professional standards

If we can look at our medical patients and after diagnosis sort them into those requiring fast-stream and those requiring slow-stream management, I believe we shall do much to improve the efficiency of the medical care of the elderly—already so large a part of our work—and we shall correct the anomalies of the present system where it is often a matter of chance whether a patient occupies a bed in one hospital costing £25 a week for his treatment, or in another costing £12 a week

I should like to thank Dr G C Kelly, of the South Western Regional Hospital Board, for his helpful criticism

Points of View

THE SEDATION AND STIMULATION OF MAN *

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People with stress, tension, and irritability feel the need for sedatives, and those with fatigue, apathy, or boredom seek stimulation

NEED FOR SEDATION

Stress—The increase in the pace and complexity of civilised urban life can be easily blamed for any increase in nervous illnesses To believe one is under stress or strain is easy and acceptable Acceptable to doctors because it explains much that cannot be otherwise explained, acceptable to patients because it excuses much that could not otherwise be excused, and to drug houses because it provides a demand for drugs that would not otherwise be demanded Yet we should not equate speed and complexity with stress and strain Cavemen probably suffered as much strain over the problem of choosing the right cave as business men suffer today over choosing the right stocks and shares

Tension—By this vague word, I mean a sensation of inward excitement, but not pleasant excitement—akin to anxiety or apprehension, but with no awareness of what is apprehended The patient with tension is waiting all the time for something important to happen " *I don't seem able to relax* "

I believe the increase of tension, too, is more apparent than real Under different names, it has troubled men for unresponsive until the arrival of the next R wave The Q-T interval may be estimated[8] from the expression Q-T$=0\,385\sqrt{C}$, where C is the interval between successive beats Ordinarily, the Q-T interval lies between 0 3 and 0 4 second, but some form of variable delay is desirable to deal with the range which may be found in clinical practice Visual indicators, in the shape of miniature cathode-ray tubes (the "magic eye" tuning indicators of radio sets) are a useful addition to the C T—one to show the arrival of the R wave, and the other to show the output from the integrator

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* Based on a paper read before the Section of Medicine of the Royal Society of Medicine on Jan 28, 1958

ELECTRODE DESIGN

Boyd and Eadie[3] describe the types of electrodes which they found most reliable In an anæsthetised patient, ordinary needle electrodes inserted in the chest wall were the best, for a conscious patient, a chest electrode (preferably earthed) and an electrode on the left leg gave the most satisfactory results A form of electrode, which might be even better for some investigations, has been perfected in the Psychological Research Laboratory of Electrical and Musical Industries,[9] for research in electro-oculography where potential differences of the order of 20 microvolts have to be detected and measured The electrodes are of high-purity silver, kept as free as possible from all contamination Contact is made to the inner skin, after the epidermis has been removed with a dental burr, the operation is painless and penetration is too shallow to cause bleeding The electrodes are held in place by suction-cups filled with saline solution, thus eliminating the various zero frequency potentials in the electrodes themselves and on the skin

In 1956, Manzotti[10] published details of another T C circuit He eliminated muscle-potential interference by using a band-pass filter, centred on a frequency of 12 cycles a second, the design is rather critical, as such circuits tend to "ring" unless heavily damped, and damping reduces the upper limit of the counting-rate Mains interference was removed by using a balanced amplifier to provide degeneration of any signal which appeared symmetrically in each input lead

An entirely new C T circuit has been devised by the staff of the Clothing and Stores Experimental Establishment of the Ministry of Supply First shown publicly at the Instruments, Electronics, and Automation Exhibition at Olympia last May, it is a telemetering system effective over a distance of up to half a mile, intended to measure the heart-rate during violent physical exercise, such as negotiating an assault course Electrode and muscle action potentials are got rid of by sampling and amplifying the electrical activity from three different areas of the body These amplified outputs are fed to a coincidence circuit, so that only the activity common to all channels—namely that of the heart—is accepted and used to pulse a transmitter Although muscle-action potentials are large and there must be some movement of the electrodes, the transmitter will produce a clean pulse for each heart beat, at rates up to 100 beats a minute The complication of three gating circuits is well worth while, because low-frequency filters and tuned circuits are unnecessary No form of integrator was fitted to the prototype C T, the rate being determined by counting the transmitter pulses as heard over a loud-speaker, or as displayed on a cathode-ray tube The pulses may be recorded on tape, together with a commentary on the activities of the subject A miniaturised version of the transmitter, small enough to go in a soldier's pack, is under development There is no reason why this particular instrument should be confined to cardiotachometry—various other physiological measurements, such as body-temperature or vapour pressure, could be transmitted—and it could be of great value in studies of industrial fatigue

ELECTRONIC CIRCUITS AND EXPLOSION RISKS

During an investigation of heat-production in electronic apparatus, Shaw[11] found that the glass envelope of a miniature valve, dissipating 10 or 12 watts, might be as hot as 250°C, and that temperatures of 150°C to 180°C are customary when the valve and its associated equipment are enclosed in a case whose cooling arrangements have been arrived at by the usual rule-of-thumb methods As the Report of the Working Party on Anæsthetic Explosions[12] recommended that 149°C should be the maximum temperature of exposed surfaces in potentially explosive atmospheres, there is a risk attached to the use of electronic instruments in such surroundings Heavy, gas-tight instrument-cases are not satisfactory, temperatures in them are bound to be high and circuit components deteriorate rapidly, and stability—an essential in high-gain amplifiers—suffers accordingly Since most valves operate at anode potentials of 250 volts or more, another source of danger, especially with capacitative circuits, is that a break in the high-tension line or the opening of a switch may produce a vicious arc even though the current flowing may be no more than a few milliamps

TRANSISTORISED CIRCUITS

Junction transistors are small, remain cold, work at low voltages, and draw minute currents circuits using them are inherently safe in the presence of flammable or explosive vapours and gases The first "transistorised" C T was described by Molyneux[13] three years ago, and he has since published details of an improved model[14] Although carrying out many of the same functions, valves and transistors are not directly interchangeable, and the amplifier of Molyneux's instrument differs from that of a valve-operated C T, since transistors are particularly sensitive to changes in ambient temperature, a compensating circuit has to be included The amplifier has a pass-band of 10–14 cycles a second, and stringent tests have shown that "double counting" will take place only when the subject carries out really energetic movements Because of the slow response of the integrator—a matter which will be discussed later—the C T incorporates a transistor oscillator to produce an audible signal for each heart beat, so that the onset of any irregularity may be detected immediately Electrical interference is kept to a minimum by the use of a wooden case and a wooden chassis A small dry battery is enough for forty hours' use before any sensible change takes place in the calibration The instrument has a high input impedance—80 kilohms—so that it can be used in parallel with a standard electrocardiograph without affecting the appearance of the trace

FŒTAL HEART-RATE RECORDING

The recording of the fœtal heart-rate presents some special difficulties, and what is believed to be the first leaflet recommends suitable passages from the Bible for those who seek peace and tranquillity

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[8] Lorenz E, Weikel, J Norton, S G *Rev Sci Instrum* 1946, 17, 276

[9] *Electronic and Radio Engineer*, 1957, 34 140

[10] Manzotti M *Electron Engng*, 1956 28, 446

[11] Shaw E N *ibid* 1957, 29, 13, 65 115

[12] *Report of a Working Party on Anæsthetic Explosions*, p 29 H M Stationery Office, 1956

[13] Molyneux, L *Brit J Anæsth* 1955, 27, 262

[14] Molyneux, L *Electron Engng*, 1957, 29 125

Perhaps one day the pharmaceutical firms will evolve the perfect drug In Aldous Huxley's novel *Brave New World*, " soma " had all the advantages of both heroin and gin and none of the disadvantages But some people may feel like the hero of that book did when he was encouraged by his mistress to take a dose " I'd rather be myself ", he said, " myself and nasty Not somebody else, however jolly " I think such an attitude is the wisest one for man to take towards his own sedation and stimulation

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Occasional Survey

CARDIOTACHOMETRY

ONCE the thermionic-valve amplifier had been applied to the electrocardiograph, the era of the delicate and temperamental string galvanometer was almost over Amplifiers have improved and new methods of recording the electrocardiogram (E C G) have evolved, but the major advances of the last two decades have been clinical rather than technical, so it may seem surprising that instruments for the accurate recording of the heart-rate are only now emerging from the laboratory stage Stable high-gain amplifiers have been available for some time, but those with a sufficiently large signal-to-noise ratio are a development of the past five or six years

In 1952, Boyd and Eadie [1] published details of a cardiotachometer (C T) for use with decerebrate or anæsthetised animals, some of the more interesting features of its design have already been noted [2] Two years later,[3] the same workers described a new instrument for continuously recording the heart-rate of a patient either lying at rest in bed or else carrying out controlled exercises while standing Boyd and Eadie found that, in spite of the experience gained with the earlier C T , many new difficulties arose, and in their article, which includes a valuable list of references to earlier work, they discuss the various means adopted to overcome them

Essentially, a C T consists of a transducer which produces an electrical signal for each heart beat, this signal, the pulse wave, which may come from heart-sounds or the E C G , is fed to a wave-shaping circuit which provides an impulse of constant amplitude for each beat A further circuit integrates these impulses with respect to time and supplies the necessary output for a visual indicator—usually a specially calibrated voltmeter, or else a graphic recorder

TRANSDUCERS

There are many different forms of transducer, each with its advantages and drawbacks The impedance plethysmograph [4] [5] measures the change in impedance to radio-frequency current in a limb as the amount of blood varies between systole and diastole, and could furnish the required input to trigger a wave-shaping circuit However, since muscle movements affect the blood-volume between the electrodes, the impedance plethysmograph is of little value unless the subject is at rest

An adaptation of the photoelectric oximeter, first described by Millikan,[6] could be used—as also could a photoelectric cell operating with light of a suitable wavelength reflected from the skin Unfortunately, the oximeter is heavy and uncomfortable, and even if it were possible to use the tiny photo-transistors now obtainable, its utility would be restricted since the cases in which the C T is most needed are often those in which the output of the heart is greatly diminished, either from disease or during some surgical procedure

A microphone on the chest wall or on the side of the neck will give a large enough output, but, once again, its use is confined to patients at rest, because extraneous noises and sounds from the friction of clothing add many artefacts to the signal The thermionic transducer is more sensitive than the conventional microphone, and its signal would need less amplification, but it is costly and equally affected by unwanted sounds

ELECTRICAL INTERFERENCE AND ITS ELIMINATION

In man, the R wave of the E C G in lead II has an amplitude of between 0 4 and 2 3 millivolts (mV)—about ten times that of the P wave, which Boyd and Eadie used in their original C T —and can, under ideal conditions and after pre-amplification, provide an excellent triggering signal for a wave-shaping circuit However, when the subject moves about, the sharp spike of the R wave disappears in a mass of interfering potentials of various frequencies and amplitudes The wave-form as actually picked up includes the E C G itself, muscle action potentials with an amplitude of 10 mV or more, 50 cycles a second interference of up to 750 mV from electrical wiring, and, perhaps, diathermy and X-ray interference of any frequency and amplitude In addition, there are various zero frequency potentials derived from electrochemical action in or under the skin or in the materials of the electrodes, and from the skin of anyone touching the patient This sounds a formidable list, but as Parker et al [7] showed a few years ago, much of the interference can be eliminated by use of some of the recognised " tricks " of the electronics engineer In their radio-electrophysiolographograph they used a small frequency-modulated transmitter, the signal from which was picked up by a receiver equipped with a number of analyser filters It was necessarily a complicated instrument—though ideal for the investigations for which it was designed—and its proper functioning depended a great deal on the electrostatic condition of the atmosphere

A capacitance-coupled amplifier is unaffected by zero frequency potentials, trouble may arise from the amplifier " blocking " from voltage transients arising from movements of the electrodes, but this can be minimised by careful electrode design Boyd and Eadie [3] found that screening and filtering would eliminate most of the other interference, but that muscle activity was still troublesome In the first version of their human C T they used a selective amplifier, resonant at 6 cycles a second, unfortunately, the circuit was unstable at this low frequency The second C T incorporated a triode phase-shift oscillator which proved both simple and reliable It is possible for the T wave to trigger this, or any other circuit with a good response at about 6 cycles a second, and so cause " double counting " If, however, the wave-shaper is provided with the electronic equivalent of the refractory period of a nerve, it can be rendered

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[1] Boyd, W E , Eadie, W R *Electron Engng*, 1952, 24 102
[2] *Lancet* 1952, i, 705
[3] Boyd, W E , Eadie, W R *Electron Engng*, 1954 26 330
[4] Nyboer J , Bagno, S , Barnett, A , Halsey R H *J clin Invest* 1940, 19, 763
[5] Nyboer, J , *in* Medical Physics, edited by O Glasser Chicago 1944
[6] Millikan, G A *Rev Sci Instrum* 1942 13 434
[7] Parker, C S , Breakell, C C Christopherson F *Lancet*, 1953, i, 1285

Ministry of Health, the Agricultural Research Council, the Medical Research Council, the Government Chemist's department, the Board of Trade, and the Nature Conservancy The advisory committee recommends whether or not a substance should be included under the Agriculture (Poisonous Substances) Regulations, and, in the case of substances not included, it may make recommendations for the safety of users and invite manufacturers to include on their label the appropriate voluntary precautions The consumer is protected by recommendations regarding dosage of material to crops and stored products, method and frequency of application, and the interval between application and harvesting The risks to livestock and wild life are also considered

Hazard to the consumer is hard to assess It is practically impossible to prove that any substance is harmless, and the committee must decide whether a few parts per million of a toxic substance ingested daily for a lifetime by a whole population is likely to harm individuals or the population as a whole It is not surprising that the committee is content to say that, subject to conditions described in the recommendations, a material " should present no hazard to consumers " So far, no cases of illness have been recorded as a result of eating food treated with any pesticide according to accepted methods, but accidental poisoning occurs from time to time For instance, Davies and Lewis [1] reported that a number of people ate bread made from flour contaminated during transport by 'Endrin', a chlorinated hydrocarbon type of insecticide In the U S.A dicophane (D D T) has been detected in the fat of persons who had had no occupational exposure to this substance, which was apparently ingested in food There is no evidence that the presence of as much as 20 parts per million in the fat gives rise to any symptoms [2] Whether it is desirable to treat food with substances which can accumulate in the tissues of man and animals is another matter, and must be assessed in relation to the benefits of the increased food production that has resulted from the use of pesticides

It is easier to advise on measures for protecting persons using pesticides, and where necessary to enforce these by legislation The Agriculture (Poisonous Substances) Act, 1952, was designed to make compulsory certain provisions for the protection of persons using toxic chemical substances in agriculture and horticulture

The committee has recommended the addition, to substances scheduled under the Act, of fluoracetamide formulated at a strength greater than 1% active ingredient, and the alkali arsenites With regard to the latter substances it recommends that the Agriculture (Poisonous Substances) Regulations should be amended to prescribe that workers who handle potato plants which have been sprayed with arsenites within the preceding ten days must wear suitable protective clothing [3]

Organo-mercury compounds used as aerosols in greenhouses already come under the regulations The current recommendation with regard to organo-mercury dry-seed dressings may need to be amended The committee has agreed that organo-mercury compounds with a vapour pressure not greater than that of ethyl mercury chloride when used alone, or as a component of dry-seed dressings, need not be included in the regulations Ethyl mercury chloride is approximately as volatile as metallic mercury [4] It is therefore volatile at room temperature, and the volatility will increase as the temperature rises The maximum allowable concentration of inorganic mercury is accepted as 100µg per c m of air, and Ahlmark [5] recommended that the upper limit for organo-mercury compounds should be 10 µg per c m In the case of the dry dressing of seeds a potential risk exists, not only from vaporisation of the organo-mercury compound, but also from the presence in the working atmosphere of dust of small-particle size It is difficult to believe that the concentration present in the atmosphere will be less than 10 µg per c m Poisoning by organo-mercury compounds causes selective damage to the central nervous system which may lead to permanent disability or death In the reported cases the most serious effects have resulted from contact from ethyl or methyl derivatives, and laboratory workers as well as those engaged in the manufacture and use of these materials have been affected [6]

Seed-dressing stations where organo-mercurial dusts are used are subject to the regulations of the Factories Acts (1937) and protection of workers in these places should be adequate, but some seed-dressing is done in less favourable conditions If the committee's advice to agricultural workers handling seed treated with organo-mercury dry dressings is followed, the hazard should be slight, but since voluntary precautions are sometimes ignored it may become necessary to make the precautions obligatory In the recommendations for protection of consumers, the suggestion that " sacks which have contained dressed seed must be well shaken " is surely bad advice unless the person doing the shaking and those in the vicinity are adequately protected

Antibiotics are being used on an increasing scale for food preservation Recommendations are made for one of these, 'Griseofulvin', for which no special precautions for the operator appear to be necessary

The experience of one employer showed that in men using 'Diazinon', an organo-phosphorus compound of low toxicity, the plasma-cholinesterase decreased even though they wore protective clothing which included gloves Investigations suggest that, possibly because of solvents or other additives, gloves may not remain impervious to organo-phosphorus compounds, and enough may be absorbed through the gloves to depress cholinesterase activity

Smallpox in the Wirral

When smallpox was diagnosed in the boy aged 2 living in New Ferry,[7] his grandmother and sister were vaccinated on April 14 The grandmother, who had been vaccinated only in infancy, had a primary take She became feverish on Monday, April 21, and on the Wednesday evening a discrete palpable macular rash appeared on her trunk and limbs The rash became morbilliform on Thursday, and papules appeared on the limbs on Friday The sister, who had not been vaccinated before, also had a primary take She became feverish on Tuesday, April 22, and on the Friday, when her temperature settled, a few papules appeared on her limbs, forehead, and neck Neither patient is generally ill, but both have been admitted to New Ferry Smallpox Hospital, smallpox virus has been isolated from scrapings from the lesions The Indian seaman at the hospital has recovered, except for a few lesions on his feet thought to be infective

Arsenic and Lead on Apples

Public-health inspectors at Coventry recently found traces of lead and arsenic on the skins and stems of two batches of apples from the Lebanon [8] The contamination is thought to have been caused by a pesticide spray The Ministry of Health reports [9] that the trade has cooperated in safeguarding against this hazard in apples from certain Mediterranean and Middle East countries by having the contaminated fruit washed, but some such fruit may have escaped detection " The elementary hygienic practice of washing all fruit before eating affords adequate protection from any hazard to the consumer peeling and coring provide an additional safeguard " fœtal C T was described by Smith[15] about a year ago Heart-sounds had to be relied upon, as it proved impossible to separate the electrical potentials of the maternal heart beat from those of the fœtus Smith admits that the instrument is not perfect, but his results were encouraging, as it proved possible to record the fœtal heart-rate over a number of hours and even during the final stages of labour A sensitive vibration pick-up was strapped to the abdominal wall over the point where the fœtal heart-sounds could be heard most clearly There was no interference from the heart-sounds of the mother, and, in twin pregnancies, it proved easy to pick up an interference-free signal from each fœtus The output from the microphone is fed to an amplifier with a voltage gain of 10^6 and a pass-band of 60–80 cycles a second, this amplifier has special characteristics to discriminate against digestion noises and uterine souffles The heart-rate is displayed as a trace on a graphic recorder

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[1] Davies, G M, Lewis I *Brit med J* 1956, ii 393

[2] Hayes W J, Durham, W F, Cueto, C *J Amer med Ass* 1956, 162, 890

[3] See Whitehead T P *Lancet*, 1957, ii 953, annotation *ibid*, p 1047

[4] Charnley, T, Skinner, H A *J chem Soc* 1951, 2, 1921

[5] Ahlmark, A *Brit J industr Med* 1948 5 117

[6] Swensson, A *Acta med scand* 1952, 143, 368

[7] See *Lancet* April 26 1958, p 906

[8] *Birmingham Post*, April 21

[9] *Mon Bull Minist Hlth Lab Serv* 1958, 18, 76

The only serious interference came from clothes and blankets rubbing against the microphone, the high noise levels of hospital wards and labour rooms gave no trouble, and any spurious pulses caused by fœtal movement were too short in duration to affect the instrument Interference with the record from movements of the patient during labour was unavoidable, but careful supervision enabled these artefacts to be recognised

Although not strictly a cardiotachometer, as it does not include any form of integrating circuit, a fœtal phonocardiograph described by Dewhurst and Mainland[16] has several interesting features intended to deal with a specific problem—namely, the determination of the presence of the fœtal heart sounds As Wood[17] pointed out a few years ago, the fundamental frequency of the fœtal heart-sound is about 16 cycles a second, varying proportions of higher harmonics are usually, but not always, present[18] Since the fundamental frequency is below the limit of audibility, the output from the phonocardiograph is fed to a graphic recorder, though a headphone responding to the higher harmonics is provided for placing the microphone An integrator was thought unnecessary as the phonocardiograph is intended purely for diagnostic purposes after the twentieth week of pregnancy The fœtal heart-sounds are picked by a crystal microphone, loaded to give a peak response at 25 cycles a second, in contract with the mother's abdomen The high-frequency response of the amplifier, which has a usable gain of 2×10^6, is purposely limited to render it insensitive to outside noises The fœtal heart-rate of 120–160 beats a minute falls just within the limits of the upper frequency response of a slightly modified commercial E C G recorder

INTEGRATING CIRCUITS

The slow response of an electronic integrator, while sometimes adequate for physiological research, is often inconvenient for clinical use where an immediate indication of a change in heart-rate can be of vital importance Manzotti[10] suggests that an accuracy of ±2 beats would be reasonable in an integrator in which 30 beats would be needed to reach 90% of a variation consisting of a sudden jump in the heart-rate from 60 to 120 beats a minute But when other physiological phenomena must be correlated with the heart-rate, the circuit must record it instantaneously, and must therefore give, at every beat, a signal proportional to the reciprocal of the time interval between that beat and the preceding one In Manzotti's C T, the computing circuit releases a constantly delayed signal for every R wave This signal displays, on the Y axis of a cathode-ray tube, a potential that decays hyperbolically and is therefore proportional to 1/time The electron beam is cut off except for the time between the R wave and its delayed signal, just at the end of the R-R interval, hence a dot can be recorded photographically which—provided the delay has been properly chosen—has an ordinate proportional to the heart-rate, as computed on the R-R time interval

At about the same time as Manzotti, Wyatt[19] described a heart-rate meter which could register 99% of the true rate in three seconds He has lately produced an instrument with an even better response[20] The heart-rate is indicated on a specially calibrated microammeter and is accurate to ±2% This performance has been attained only at the expense of considerable complexity which would probably preclude the use of the instrument outside the laboratory

Technical finality has clearly not yet been reached in C T design The gated amplifier of the Clothing and Stores Experimental Establishment design seems to have great promise, especially if it could be followed by an integrator with a quick response giving a visual numerical display on the lines of various scalers and counters now produced commercially for counting atomic disintegrations

Public Health

PESTICIDES

NEW pesticides may be poisonous, not only to persons engaged in their formulation, manufacture, and application, but also to the public who consume products treated with them The problem of protection has been dealt with by different methods in different countries

In the U S A the Food and Drug Administration (F D A) is responsible for advising manufacturers about new substances, including pesticides, and establishes limits for the amounts of any added material which may remain in food as residue from spraying or other treatment It has power to seize and examine food to ensure that regulations are not infringed In Great Britain control depends largely on voluntary cooperation between the pesticide industry and Government Departments

Negotiation between the industry (represented by the Association of British Insecticide Manufacturers) and the Ministries of Health and of Agriculture, Fisheries, and Food has led to agreement on a procedure whereby the manufacturer or distributor of a new pesticide, or of a new formulation of a known pesticide, gives notice voluntarily of the intention to market the new product, together with the fullest possible particulars of its properties and use, so that Government Departments may advise on measures to protect both workers and consumers The resulting recommendations do not have the force of law

The data are considered by an advisory committee (set up by the Government in 1956) and a scientific subcommittee, which comprise representatives from the Ministry of Agriculture, the Department of Agriculture for Scotland, the Department of Health for Scotland, the

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[15] Smith D H *ibid* p 132

[16] Dewhurst, D J, Mainland, J F *ibid* p 340

[17] Wood, M C *ibid* 1953 25, 90

[18] Gunn, A L, Wood, M C *Proc R Soc Med* 1953, 46, 85

[19] Wyatt, D G *J sci Instrum* 1956, 33, 410

[20] Wyatt, D G *Electron Engng*, 1957, 29 336

Letters to the Editor

CEREBRAL PALSY

Sir,—Your leader of April 19 raises a number of questions, the most fundamental of which is that of definition To define " cerebral palsy " is important, not only because people with it have " certain needs in common ", but as an essential preliminary to research and exchange of information It is also essential that any definition is acceptable equally to neurologists, pædiatricians, and others and that they adhere to it in discussing the topic.

There are certain points which your definition of " cerebral palsy " as " a congenital motor deficiency that is not progressive " does not make clear Are we to include " motor deficiency " caused by congenital lesions of the cord, nerves, muscles, bones, and joints? Are we to exclude disorders acquired in the neonatal period, such as those following severe jaundice of the newborn? Is the " motor deficiency " always, or even frequently, congenital—that is, present at birth? Is the " motor deficiency " never progressive? (What is not progressive is the lesion, its signs and symptoms change with development as emerging functions interact with older dysfunction) Is " motor deficiency " appropriate for cases which essentially show unwanted movements?

To define " cerebral palsy " cannot be easy, for the cases it includes are not all identical In trying to arrive at a useful definition of cerebral palsy certain points need to be considered

(1) It is a palsy or *motor disorder*

(2) It is the result of a lesion of the *brain*

(3) Only disorders resulting from *non-progressive lesions* are to be included

(4) The damage of the brain may be from intrinsically or extrinsically caused development disorder (occurring in fœtal life or after birth) or may be perinatal, paranatal, or postnatal in origin

(5) The moment of birth as a criterion in definition has little usefulness, for birth is only an incident in the long course of prenatal and postnatal development of the nervous system What is important is the stage of development of the child at which the damage responsible for the motor disorder occurs, the word development here implying that of the intellect and personality as well as of the central nervous system.

During the past year a number of interested people have met at the Little Club to discuss a memorandum on the terminology and classification of " cerebral palsy " The memorandum is not final but it seems worth while to set out below the definition of " cerebral palsy " arrived at together with its explanatory footnotes The participants in the discussions were Dr N S Alcock, Dr J Bates, Dr E A Carmichael, Dr J Crosland, Dr P R Evans, Dr M C Joseph, Dr M J McArdle, Dr D McDonald, Dr I C K Mackenzie, Prof A A Moncrieff, Sir Charles Symonds, and the undersigned

London, S E 1

R C Mac Keith
P E Polani

DEFINITION OF " CEREBRAL PALSY "

In the present state of our knowledge the term " cerebral palsy "[1] is taken to imply a persisting qualitative motor disorder[2] due to non-progressive[3] damage[4] of the encephalon[5] occurring before the growth of the central nervous system is complete Because the cases it includes are not all identical from clinical, ætiological, and morbid anatomical aspects, the term " cerebral palsy " is not an exact one In scientific usage, as we learn more about each, the names of individual disease entities within the group should be used Meanwhile, however, for research purposes the term " cerebral palsy " is useful in the study of a group of conditions often of obscure origin affecting the brain and arising in early life. A strict definition is necessary and should be adhered to if the term is to be used for research and in the exchange of information

On the other hand, in common usage the term has administrative usefulness and a practical value largely because the affected children often have certain special motor, intellectual, and emotional difficulties in common and so have certain special therapeutic and educational needs The effect on a child of a motor handicap of cerebral origin, present from very early in his development, is very different from that of a similar disorder occurring later For the purposes of definition a time limit has to be fixed The definition of " cerebral palsy " therefore proposed is

> a persisting qualitative motor disorder appearing before the age of three years, due to a non-progressive damage of the brain

Sir,—In the two articles and the leader in your issue of April 19 only the briefest mention is made of the place of surgery in the treatment of limb deformity Out of some 10,000 words less than 200 were used to discuss surgical treatment and these mostly to describe a single case of an operation for flexion contracture of the knees

The repeated disappointments which followed operations in the past and in particular the misadventure of Royle's sympathectomies caused such gloom to surround the value of surgery for the correction of limb deformities in cerebral palsy that there are today undoubtedly many patients of good intelligence and personality who struggle about with grotesque skeletal deformities such as would not be tolerated in almost any other disease

Dr Palmer states that he has no doubt that " there is a place for surgery in the adult spastic, but this must be very carefully considered beforehand " But the need for careful consideration of an operation should not act as a bar The planning of an operation is no problem special to cerebral palsy, but is called for in the judgment of any reconstructive operation, whether it be for hallux valgus or for the improvement of an osteoarthritic hip-joint

There is no doubt that much can already be done by operations to assist many patients suffering from limb deformities consequent upon cerebral palsy, and much can be learnt by carefully planned and staged procedures, but this is not the place to discuss these in detail

What is now urgently needed is a *systematic* programme to study the possibilities and limitations of surgical methods for the relief of limb deformities in cerebral palsy, which could in time produce results comparable to those achieved in dealing with the effects of poliomyelitis It is to be hoped that the programme of vaccination against poliomyelitis will release the surgical skills and time for this purpose in the not too distant future Some start should now be made

London, W 1

Lipmann Kessel

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[1] The adjective infantile before " cerebral palsy " is not considered to be necessary as the term has no place in the neurology of adults

[2] This excludes such quantitative disorders of movement as might be met with in mental defectives

[3] The clinical evolution with the passage of time seen in cases of " cerebral palsy " has usually been explained by nervous system growth and maturation with the resulting emergence of new functions and their interaction with old deficits Some workers think this explanation inadequate and suggest that some of the changes in clinical findings could be ascribed to progressive pathological lesions

[4] The damage of the brain may be from intrinsically or extrinsically caused development disorder (occurring in fœtal life or after birth) or may be perinatal, paranatal, or postnatal in origin

[5] The brain, that portion of the central nervous system above the foramen magnum

In England Now

A Running Commentary by Peripatetic Correspondents

I HAD prided myself on being perhaps the first doctor in Britain to use nylon syringes They proved invaluable and the breakage-rate dropped to zero almost overnight The pleasure of having syringes which bounced was never-ending Now I may prove to be the first to give them up

At the end of my new secretary's afternoon duties she left the place tidy for evening consultations, with one nylon syringe on the steriliser and five inside Those who, a few hours later, met all the dark smoke filling the rooms and corridors thought at first that the house was on fire The five syringes have gone—are nowhere But the inside surfaces of the steriliser and the edges of its lid bear a thick hard coating of glossy black The nearby walls and ceiling look even more off-white than before For strength and tenacity let me recommend distilled nylon Hours of scrubbing and every solvent the dispensary, the kitchen, and even the garage could produce have made a quite tiny impression on the dark layer My secretary and I reckon that with diligence and detergents the steriliser may be clear by Christmas

My unhappy wife cannot rid our house of its new odour It reminds me of those window-jammed homes I hate to visit, the sort of house into which I do not take my hat lest I have to put it down on one of its uninviting surfaces The modern-minded women among my patients say that they are familiar with the new odour of the professional rooms Yes, as they give their little disgusted domesticated sniffs, yes, they had met it when the iron was too hot for their nylon frilleries The material under the iron just disappeared, or rather was converted into slight stickiness of the iron plus a smell I have even been told of a girl who wore her nylon nightgown too close to a fire and suddenly, without flame, found herself naked

My syringes have gone, but oh, how their memory lingers on!

* * *

I am glad to see that the new edition of *Martindale* retains my old friend the Chelsea Pensioner I found this versatile old soldier several editions ago quite by chance He has lent his name to Confectio Guaiaci Composita, which must be a carminative of remarkable power if the synonym is to be believed One day I must write

℞ Conf Chelsea Pensioner
Mitte ℥ii N P

That should lift a few eyebrows if nothing else

* * *

Clearing out the attic I found some old medical objects of my grandfather's, and rather than throw them away I offered them to a dealer

After handling one in a cursory manner, his speculative eyes slowly looked me up and down "You are a medical man, I presume?" I nodded agreeably and awaited identification of the article He wheeled round, stuck his head into the hatchway, and shouted, "Did you hear that, Bert? Medical gentleman here never heard of a fleam—and a three-bladed one, too!" He was answered by a raucous Cockney yell of derision from the vaults below Having thus drained me of confidence, he continued briskly "Now, sir—these articles—kindly name your price" I ventured 2 guineas After all, my Green Line fare to Church Street was *7s 6d* "I'm afraid you are wasting our time, sir *17s 6d*," he snapped and made to move away I disliked the thought of approaching another dealer, and, after I had pocketed the handful of silver, he became more expansive Slowly sucking his yellow teeth, he sighed "Of course, I shall have to clean them up and another nuisance, you've lost the locking nut for the Tribulcon Bert," he roared, "fix this hinge and tell me if it's a Tribulcon or an Alphonsine"

My ignorance apparently offended him, but taking a firm grip on his patience and speaking slowly, he explained "The early Napoleonic bullet-extractor was called an Alphonsine after some surgeon-general The Tribulcon was a bit earlier Both damaged the tissues more than the bullet Now, I believe this here is a Freeke's tourniquet of about 1820—you've ruined the cog-and-wheel mechanism—and the handle to tighten the band is very loose They were never satisfactory I ought to ask you for my money back This sort of blow-lamp is an early antiseptic steam-spray producer" My heart sank as he exhaled on the name-plate and, with a vigorous rub, disclosed with fearful clarity *for Prof Lister by J Gardner instr mkr Edin*

"What a pity you haven't got the scarifier," he sighed, as he prised open the small silver box from which two rusty needles fell out "It could be a Jenner—probably not an original, though *E Jenner, Sgn, Berkely*, looks faint and genuine enough" He smiled whimsically as his eye caught the fleam again and he was just about to laugh in my face when he braced himself to say, in a censorious tone, "Junk—sheer junk! Top prices paid and I still have to make an honest living" He poked at the heap in mock reproach with a dirty fingernail "Oh well, I suppose the private collectors and the museums will fight for them" His tone was tinged with triumph and I was halfway through the door before he remembered to cry, "Have you any more? Top prices" But I waited no longer and, retiring to the nearest espresso, pondered over a cup of black coffee on my amazing ignorance

* * *

Your peripatetic tale about the lost bicycle pedal reminds me of my failure in World War I to interest the powers that be in the great saving of steel that could be effected by providing members of mounted regiments and others wearing spurs—e g, G O C London Command and some others of the Military Police—with only one spur instead of two The argument, based on anatomy, is of course that if you get one side of the horse going in the right direction, the other side of the horse will go the same way And what's wrong with that, I ask you? Alas, I couldn't induce any general to think that he thought of it first And so it wasn't done

* * *

Pop was moved into the sideward of the female surgical ward with certain misgivings It had been used for men before but each occasion had produced such a violent reaction in the sister that we had sworn never to repeat the practice Pop, also, was probably not going to be the easiest patient to nurse, for he was to have his remaining leg amputated because of senile gangrene

Surprises were not long in coming The next morning on the round we were told that he was "a dear" The afternoon before he had asked the librarian for a book by "that Dickens chap", and since then he has read several of this author's larger tomes, which by the look of them had not been off the shelf for many dusty years The delay in healing of his stump, while not being surgically satisfactory, has proved so socially to the sister—"The first man I've had in there whom I can tolerate"—and his protracted convalescence has helped his family through the recent cold spell Mum comes in with a cheery "Well, Dad, how are you today?" and the interchange of news goes on for about five minutes After this the comfortable armchair by the fire is amply filled and Mum dozes off leaving the rest of the conversation to her daughter Wednesdays, Saturdays, and Sundays are the best days because really it does take longer than twenty-five minutes to get warm right through

* * *

Letter from a mother-to-be to her G P

During the past few months I have consulted many experts about the safest way to have a baby *Some say this, some say that.* Some induce, some wait Some are for Cæsarean, some are for forceps, some are for trial Some weigh Some give salt, some say it's poison Some transfuse, some don't Some say it's dangerous to have a baby in hospital because of sepsis, others that it is dangerous to have a baby at home because of lack of asepsis What *is* a poor woman to do?

The G P's reply

Get a good midwife to hold your hand and rub your back—that *is* essential

Thank God my rhesus-negative wife produced our four yellow babies 13 to 20 years ago—in ignorance of what the experts think is the "safest way" Either she or I would have died of anxiety, and I'm not sure we should now have four rather nice children

As regards malaria, the present anti-larval and hygienic measures have been so widely applied, aided by the much improved methods of drug prophylaxis and treatment, that a state of affairs has been created where the malarial anæmia, with which I used to be so familiar, exists no more. I remember in particular a group of Arabs from the Hedjaz in hospital in Cairo in 1916 They were one and all suffering from such a severe form of anæmia of the pernicious type that they became the subject of hæmatological studies by the contemporary blood experts In some few the spleen was palpable

However, after careful scrutiny of their blood by the thick-film method, scanty crescents of the subtertian parasite were found in all and they recovered after long-continued quinine therapy

London, W 1 PHILIP MANSON-BAHR.

ABSENCE FROM WORK ON A MEDICAL CERTIFICATE

SIR,—I write to support the statement of Dr Gough (April 19) He asks employers to accept a written statement from employees concerning their sick absences rather than demanding a doctor's certificate.

This company pays all clerical and factory employees for absence due to sickness Twelve months ago we dispensed with doctors certificates for any absence of less than four days On return to work after illness employees now report to the nurse in the works surgery and sign a declaration that their absence was due to genuine sickness

This scheme, which is greatly appreciated by the employees as well as by the local doctors, has in no way been abused and the absence due to sickness has not increased.

Wm. R Warner & Co Ltd.,
Eastleigh, Hants.

H. WOODHOUSE
Personnel Manager

PENICILLAMINE AND DIMERCAPROL

SIR,—I have read with interest of Dr Aposhian's studies (April 19) on the relative efficacy of B.A.L and penicillamine in protecting rats against mercuric-chloride poisoning He criticises my work on the relative activity of these two compounds in mobilising copper from patients with Wilson s disease [1] on the grounds that the two drugs were not given in equimolar amounts or by the same route.

May I suggest to Dr Aposhian, first that penicillamine and B.A.L should not be compared on a molar basis but in terms of available sulphydryl groups—i.e., one molecule of B.A.L (M.W. 124) to two molecules of penicillamine hydrochloride (M.W. 205 2), approximately 1 unit of B.A.L to 3 3 of penicillamine HCl. On this basis he will find, if he reads my paper again and carefully, that cases 3, 4, and 6 were given approximately comparable doses of these two compounds. In each case the response, in terms of increased copper excretion in the urine, showed that the penicillamine was a very much more powerful cupriuretic agent than B.A.L.

Second, in clinical practice, as opposed to animal experiment, it is ridiculous to limit the usefulness of a new treatment by scaling it down to the limitations of the old. To compare the activity of B.A.L and penicillamine in man why reduce the dose of the latter and give it parenterally, why not raise the dose of B.A.L so that it is comparable to the maximum tolerated dose of penicillamine (around 4 g) and give both by mouth? The procedure would be just as logical

Finally I suggest that Dr Aposhian has tumbled into the old pitfall of trying to argue direct from the experimental animal to man. From his results with mercuric-chloride poisoning in rats he is attempting to draw valid conclusions about copper intoxication in man, a hazardous procedure. From the patient's point of view the usefulness of a drug can be decided only in terms of the response obtained to the maximum tolerated dose.

Department of Experimental Medicine,
Tennis Court Road, Cambridge.

J. M. WALSHE

PLASTIC BAGS FOR STORING AND TRANSFUSING BLOOD

SIR,—The article by Dr Dudley and his colleagues (Feb 8) is of great interest to those of us in the United States who have been concerned with the development of improved blood-transfusion equipment. The studies reported undoubtedly represent a sincere effort to compare plastic and glass containers, and at first glance the conclusion that red cells are no better preserved in plastic than in glass seems to be supported by the experimental data.

I feel it my duty, however, to point out that the experiments reported did not truly compare the preservation, during refrigerated storage, of red cells collected in plastic bags and glass bottles

The solution used in the bottles (A.C.D formula A, *U S.P*) was transferred from the plastic bags to the bottles, presumably shortly before collection of blood This solution was autoclaved in the plastic bags and had been exposed to the plastic up to the time of use. It was not autoclaved or stored in the bottles in which the blood was collected. Thus the survival experiments of the bloods collected in the bottles cannot reflect deleterious effects on red cells of changes taking place in the solution on long exposure to glass There is increasing evidence that an interaction between contained solutions and glass surfaces does take place under such conditions

On Oct. 12. 1957, a conference on the Deterioration of Parenteral Solutions was called by the National Research Council in Washington, D C. At that conference a report on particulate matter in intravenous fluids was presented from the Walter Reed Army Institute of Research Using an instrument primarily designed for red-cell counting, it was found that solutions of saline, dextrose, and dextrose plus saline, dextran, and A.C.D , which had been stored for varying periods of time, registered particle-counts up to a million per 100 ml. These particles were found to be silica Precipitation of fibrin from whole blood by means of finely divided glass is often used. Such a reaction may well account for the frequent finding of " sludging " of red cells in blood collected in bottles. This is destructive to red cells of stored blood, as shown by the elevation of the hæmoglobin content of plasma

In contrast the A.C.D solutions processed in plastic bags had particle counts of less than 10 000 per 100 ml. Widespread experience has shown hæmoglobin levels of plasma of blood collected in plastic bags to be consistently lower than that of blood collected in glass

It may therefore be truthfully said that the experiments reported merely demonstrate the excellent stability of A.C.D solution autoclaved and stored in plastic containers

No claim has ever been made that A.C.D blood collected in plastic bags could be used routinely beyond the 21-day limit prescribed by the Minimum Requirements for Human Blood (Citrated) [1] of the National Institutes of Health. In the article by Walter [2] referred to by Dudley et al in eleven experiments the post-infusion survival of the red cells of blood stored 21 days at 4 C ranged from 66 to 93%, averaging 84 %, certainly a very safe and satisfactory level, even for multiple transfusions

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1 Walshe J M. *Amer J Med* 1956, 21 487

[1] Federal Register Department of Health, Education and Welfare, Public Health Service 42 CFR, part 73, 11 Biologic Products, Whole Blood (Human) p 68[illegible]

[2] Walter C. W., Button, L. N., R[illegible], R. E. Jr *Surg Gynec. Obstet.* 1957, 105 315

SIR,—In your leader of April 19 you refer to the excellent work of our two national societies in the field of cerebral palsy

We think your readers may be interested to know that the medical advisory committees of the two societies recently met, under the chairmanship of Professor Moncrieff, to discuss some common medical problems and it is proposed to hold similar meetings from time to time The two societies are also planning to appoint a joint educational advisory committee We believe that the welfare of spastics and the work of both societies will benefit considerably from such joint meetings and discussions on matters of common concern

13, Suffolk Street,
Haymarket
London, S W 1

D E WHEELER
Chairman of Executive Committee,
British Council for the Welfare of Spastics

28, Fitzroy Square,
London, W 1

I D DAWSON SHEPHERD
Chairman of the National Spastics Society

"THESE DYING DISEASES"

SIR,—With the first few words of Dr Vickers' letter (April 19) I agree Mr King's article was timely and should be taken to heart by those who are responsible for anti-venereal arrangements in this country To those with sufficient knowledge to understand the implication of the facts Mr King has brought to notice, the prospects of combating venereal disease in this country must appear indeed gloomy He has shown a steady rise in antibiotic-resistant gonorrhœa and of non-gonococcal urethritis, which is doubtless becoming increasingly resistant to the antibiotics being, often blindly, lavished upon it And all these diseases are being spread at a greater rate than formerly by reason of the greater invasion of the country by immigrants

These alone are sufficient to merit grave concern As regards syphilis, Mr King has pointed out a possible fallacy in the inference to be drawn from the figures relating to new cases seen at the clinics when he says

> 'The main antisyphilitic remedy is used freely for many other conditions Possibly this helps to prevent the late serious effects of syphilis, but it may suppress information which would help us to estimate the extent of the problem "

We may, in fact, be in a fool's paradise in respect of this disease

With the remedy suggested by Dr Vickers I emphatically disagree, and that is on the basis of half a century's experience of the problem from most angles—laboratory, clinical, social, and administrative, both local and general As adviser on venereal diseases to the Ministry of Health, I saw, in the venereal-diseases treatment centres working under the Local Government (Venereal Diseases) Regulations, these diseases treated by general physicians, surgeons, gynæcologists, dermatologists, genitourinary specialists, and other kinds of specialists and can say without any hesitation whatever that in those hands, however skilful they might be in their own branch, with very few exceptions the result (so far as ridding the patients of their infections and stopping their danger to the community was concerned) was bad I have often wondered why these specialists in other branches accepted charge of venereal-disease clinics, and have sometimes remarked, at the end of a session which the medical officer spent seated at a desk writing " Rp " on successive case-sheets, that he must find it very boring Dr Vickers contrasts venereology with specialties concentrated on particular parts of the body and seems to think there is something unnatural about it, but what about tropical diseases, which are analogous to venereal diseases in being like one another in the circumstances of their contraction?

Dr Vickers sees little likelihood in young men taking up venereology He is probably correct in the present circumstances, particularly when those responsible for the arrangements for dealing with what is really a serious national problem take such a superficial view of the position as to talk of " these dying diseases "

London, S W 1 L W HARRISON

SIR,—The letter by Dr Vickers about the future of venereology seems to me to have been based on a misunderstanding of the fundamental argument in Mr Ambrose King's article There is, as far as I am aware, no evidence that the service is " slowly but inevitably disintegrating " In 1956, 98,212 men and women attended the venereal-disease clinics of England and Wales for the first time The fact that so many people should seek advice and help does not appear to indicate that the service is disintegrating

With regard to the recruitment of young doctors, the major problem here is surely one of confidence in the future of the service If consultant posts which become vacant are not filled or are filled with a reduction in the number of sessions it will obviously be difficult to persuade competent young men that their future lies in venereology In some areas the spectacle of consultant work being carried out by S H M O s and even persons who have no special training in the subject is hardly encouraging The solution of the recruitment problem lies in the hands of the regional boards and the boards of governors of the teaching hospitals Only if posts are filled by trained venereologists when they become vacant will entry into the specialty be stimulated and the future of the service assured

Patients attending venereal-disease clinics have many special problems, both physical and psychological, and special training and experience is needed to handle them When those who have or think that they have venereal diseases are dealt with by persons without adequate training and interest in the subject, they are frequently mismanaged

London, W 8 R D CATTERALL

HOOKWORM AND ANÆMIA

SIR,—The communication on hookworm and anæmia by Dr Meiklejohn and Dr Passmore in your issue of April 19 is very opportune, for I am one of those who are in mild disagreement with some modern high-powered hæmatologists who would ascribe most forms of anæmia in the tropics to dietetic causes, thereby trying to debunk the role of the ancylostome and the subtertian malaria parasite as the main causes I feel certain that they could not have done so had they lived as long as I have and been with me fifty years ago

There is no doubt that there is a racial factor The Fijians, who are heavily infected with hookworms (27 8%[1]), seldom, if ever, suffer from anæmia—and this has been verified by Wills and Bell[2] On the other hand, the Indians who are domiciled in Fiji frequently do, and I saw many at necropsy there in 1910 Similarly in Ceylon, in 1912, I performed such an examination in a Tamil where death was due to intestinal hæmorrhage from petechiæ throughout the small intestine This specimen, together with the adherent ancylostomes, was brought back to the museum of the London School of Tropical Medicine

There was another which springs to mind in a young Tamil labourer who died from acute heart-failure on climbing a hill, and in him, too, the hookworm anæmia was so severe that his hæmoglobin was about 15%

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1 Bahr P H Res Memoir no 1, London School of Tropical Medicine, 1912

2 Wills, L , Bell, M E *Lancet* 1951, i, 820

As regards malaria, the present anti-larval and hygienic measures have been so widely applied, aided by the much improved methods of drug prophylaxis and treatment, that a state of affairs has been created where the malarial anæmia, with which I used to be so familiar, exists no more. I remember in particular a group of Arabs from the Hedjaz in hospital in Cairo in 1916 They were one and all suffering from such a severe form of anæmia of the pernicious type that they became the subject of hæmatological studies by the contemporary blood experts In some few the spleen was palpable

However, after careful scrutiny of their blood by the thick-film method, scanty crescents of the subtertian parasite were found in all and they recovered after long-continued quinine therapy

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Department of Experimental Medicine,
Tennis Court Road, Cambridge

J M WALSHE

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[1] Walshe J M *Amer J Med* 1956 21, 457

PLASTIC BAGS FOR STORING AND TRANSFUSING BLOOD

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[1] Federal Register Department of Health Education and Welfare, Public Health Service (42 CFR, part 73, 1) Biologic Products, Whole Blood (Human) p 6540

[2] Walter, C W , Button, L N., Ritts, R E., Jr *Surg Gynec Obstet* 1957, 105, 315

Strumia[3] reported red-cell survival by the ^{51}Cr method of blood collected in A C D in bottles and in plastic bags, and stored for 21 days at 4°C This series comprised 9 glass bottles and 31 plastic bags obtained from four American manufacturers The mean values for bloods in plastic ranged from 62 to 87%, averaging 78%, whereas the average value in glass was 70% Dudley et al , referring to Strumia's article, state " these results were obtained from two autotransfusions and one transfusion with a compatible recipient "

The rate of deterioration of red cells of A C D blood is not a linear function of storage time, but becomes increasingly accelerated after about 2 weeks of storage, so that the red cells are unfit for use after 25–28 days after collection[4] No comparative values at a 21-day storage period were reported by Dudley et al The finding of no improvement of preservation of red cells in plastic over glass at a period when A C D blood is intrinsically useless, and may well be dangerous, is not very helpful for the clinician

Except for its importance to the military, a "dating period" in excess of 21 days is of no great significance in modern blood-transfusion practice It is our experience that blood is usually scarce and turnover rapid, so that a large proportion of bloods are issued within 10 days of collection This is very fortunate for the patient Consideration of factors other than red-cell viability are far more important in the safe and efficient conduct of blood-transfusion

Adherence to aseptic techniques in collection, processing, and administration is of prime importance

All rigid containers with rubber closures require puncture While the risk of contamination incident to collection (by trained personnel) is undoubtedly small, once the protective covering of the stopper has been pierced, that area is potentially contaminated Braude[5] showed that re-entry by puncture of the stopper carries a real risk of introducing microorganisms into the container All refrigerators are contaminated areas Pittman,[6] in reviewing fatal reactions resulting from administration of contaminated blood, found the gram-negative psychrophiles to be the most common causative organisms

This danger is so well recognised by the National Institutes of Health[1] that sampling by piercing the stopper, except for administration of blood, is forbidden Dudley et al 's remarks, " particularly those who object to opening bottles for samples ", suggests a truly alarming state of affairs

In the fabrication of the type of bag investigated, the donor tube with attached shielded needle is attached to the bag, and the assembly, with its contained solution, is autoclaved as a unit This reduces the risk during collection to the minimum of piercing the skin for phlebotomy The outlet ports are protected by sealed plastic tabs until the moment of assembly with the giving set, thereby eliminating direct contamination during refrigeration The risk of airborne contamination is also reduced, since the donor tube is filled with solution to the needle tip, and with proper technique no air can enter the tube before phlebotomy

Unfortunately, we have no record in this country of the rate of contaminations of bloods, or of the prevalence of pyrogenic reactions, since there is no requirement that reactions be reported Reaction rates with bottle-collected blood are estimated at 2–5% 6669 bloods were transfused from plastic bags in 1951–55, and of these 5525 were cultured The percentage of positive cultures was 0 53, and the percentage of pyrogenic reactions following infusion 0 83[2]—this is evidence of the superiority of the plastic bag over glass bottles in point of safety

The integral donor tube remains with the bag, and when serially numbered provides positive identification of blood and pilot sample at all times *Isolation of segments by dielectric sealing provides for* multiple sampling without entry of the container, and hence repeated cross-matching can be done with no risk of contamination of the residual blood In like manner samples for culture[7] can be obtained with complete safety at any period of storage

Dudley et al state " its routine use would confer minor advantages such as freedom from the danger of air embolus " Schmidt[8] has recently published case-histories of donors who suffered air emboli during collection of blood in gravity bottles Accidental occlusion of the air-vent permitted pressure to build up within the bottle so that air was forced into the donor's vein on release of the tourniquet Air embolism is a definite possibility when air is introduced into a bottle to speed administration, and this type of accident is commoner than is generally conceded Neither type of accident can occur with plastic bags since they require no venting, for taking or giving, and administration is hastened by external pressure

The plastic bag tested was designed not as a substitute for the glass bottle, but to free the practitioner from the limitations in the administration of *all* clinically useful components of blood imposed by rigid containers The vacuum or gravity (venous occlusion) bottles currently used in the United States were designed to meet the emergency of establishing an overseas whole-blood programme during World War II, and performed yeoman service They were intended only for the collection, transport, storage, and administration of whole blood, and not for subdivision into components

No successful widespread programme has ever been established for salvaging of red cells for clinical use from whole blood collected in glass bottles During World War II, the Korean action, and subsequently, all of the red cells of blood collected primarily for plasma have been discarded, and this has been the fate of over 15,000,000 units of blood collected in the United States

It has been known since 1947[4] that the survival of red cells of A C D blood from which the plasma has been removed within 24 hours after collection is at least equal, after 21 days of storage, to that of red cells stored as whole blood for a similar period This finding has recently been confirmed by the ^{51}Cr method on blood collected in plastic bags[9] *With suitable transfer bags, supernatant plasma can be* expressed from the collection bag and the residual cells can be usefully used for the full 21-day dating period

The indications for the use of separated red cells are now firmly established[10] *In current practice* about 30% of transfusions at the Peter Bent Brigham Hospital are of separated red cells All patients needing transfusions for the maintenance of a chronically depleted red-cell mass, or in whom the administration of whole blood involves the danger of circulatory overloading, receive separated red cells

Since most platelets are contained in the expressed plasma, and since, by proper manipulation, the buffy coat of centrifuged blood may also be discarded, sensitisation by platelets[11] and leucocytes[12] can be *minimised* *This is of* extreme importance to the patient needing repeated restoration of red-cell volume

The plasma harvested in the separation of red cells expands the donor panel Storage of plasma at room temperature for 6 months virtually eliminates the transmission of virus of homologous serum jaundice[13,14] Since this plasma can be pooled, it becomes available for emergency use without typing

The treatment of thrombocytopenia with infusions of platelet-bearing plasma or concentrated platelets is *now fully* established The percentage of platelets found to be viable (remaining in the circulation for from 2 to 5 days), when prepared in several types of equipment, was as follows[15]

Siliconed syringes, direct transfusion 80–90%
Fresh (1 hour) blood in plastic in A C.D or sodium edetate 75–80%
Platelet-rich plasma, plastic bag 60–65%
Platelet concentrate, plastic bag 50–55%
Fresh blood glass, gravity 15–20%
Stored blood (24 hours) glass 0

The flexibility of plastic equipment renders it most suitable for preparation of platelets for infusion

We feel that the incorporation of highly versatile plastic equipment into our practice of blood therapy has not only resulted in great economy in the use of blood but has often been life-saving in cases which would have been helpless to the physician with only conventional equipment

Finally, with regard to the minor technical difficulties mentioned, I believe it was Benjamin Franklin who said that " All arts are capable by practice of improvement "

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JOHN G GIBSON

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MITRAL VALVOTOMY AND PREGNANCY

SIR,—My letter (April 5) may not have been expressed with sufficient clarity, but Dr Wade and his colleagues (April 19) have misinterpreted the comments on their paper

The problem of mitral valvotomy during pregnancy is discussed and then in the last paragraph it is stated that surgery during pregnancy is undesirable unless there is evidence for tight stenosis based on severity of symptoms before pregnancy began or objective evidence of long-standing pulmonary hypertension It is not stated that both these criteria should be present

Actually in our overall experience of patients proved to have tight stenosis electrocardiographic evidence of right ventricular hypertrophy by conventional standards in the conventional leads has only been present in 34% (although by slightly more liberal criteria and including the right-sided V leads in 65%)[1] The point at issue is this—if operation is advised solely on the basis of symptoms which first arose during pregnancy then, from our experience and that of others, there will be many cases in which the degree of stenosis found will be relatively mild and insufficient for the patient materially to benefit from valvotomy

In fact, Wade et al state in their paper that 4 of their 12 patients had only moderate stenosis which "could have been managed medically" Certainly pulmonary œdema may occur during pregnancy without tight stenosis, but in our experience such cases can always be managed medically and after the confinement undue dyspnœa on exertion disappears We do not agree with Dr O'Driscoll and Dr Drury (April 12) that operation should be deferred until after delivery because, as Wade et al point out, pulmonary œdema from tight stenosis may be fatal despite initial response to medical treatment

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University of Edinburgh

R W D TURNER

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A NEW SULPHONAMIDE

SIR,—Dr Sklař (Feb 1) and Dr Platt (March 1) have written about their experiences with 'Sethadil' (sulphaethylthiadiazole), a sulphonamide recently introduced to this country This preparation was in use in a Naval hospital during the winter of 1957–58, and all cases of acute follicular tonsillitis were given a course for 3–5 days, hæmolytic streptococci were isolated from a single throat swab in fourteen out of forty-five cases and the average duration of sickness was 8 9 days (range 3 to 35 days), assessment of cure being clinical and not bacteriological Sethadil was well tolerated and there were no toxic effects

A review of cases admitted to the same hospital during the previous winter, 1956–57, revealed very similar results with other treatments During this period forty-six patients were under treatment and the form of therapy was dictated by the admitting medical officer, in this series hæmolytic streptococci were isolated in nineteen cases after a single throat swab The average duration of absence from duty of nine treated with aspirin gargles was 9 4 days, of eleven treated with aspirin gargles and dequalinium ('Dequadin') lozenges 9 5 days, of sixteen treated with parenteral penicillin 10 9 days, of six treated with parenteral penicillin and dequalinium lozenges 9 7 days, and of two treated with trisulphonamide tablets ('Sulphatriad') and dequalinium lozenges 8 days, in addition two patients treated with parenteral penicillin and then either streptomycin or aureomycin were sick for 8 and 10 days respectively The average period of sickness of all forty-six patients was therefore 9 0 days (range 3 to 21 days)

Parenteral penicillin has long been regarded as the treatment of choice in tonsillitis since its use is undoubtedly associated with a lessened risk of rheumatic fever and other complications, an advantage not obtained with sulphonamides However, where the risk of complication is negligible or there is a danger of penicillin sensitisation, a satisfactory response can be obtained with Sethadil

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London, S W 1

J M CLIFF

INTRATHECAL PHENOL FOR INTRACTABLE PAIN

SIR,—Following the excellent and comprehensive article by Dr Nathan and Dr Scott (Jan 11), Dr Allan Brown's comments (Jan 25) on intrathecal phenol for intractable pain are of considerable interest I agree that "until a sufficient period of observation has been completed it would seem to be prudent to restrict the intrathecal use of carbolic acid dissolved in myodil to the relief of pain of malignant disease"

I do wonder, however, whether he has been led to the same conclusion as myself about one of the underlying reasons for such uncertainty I pointed out[1] that, in late cases of carcinoma, the action of intrathecal phenol was delayed by areas of growth in roots and ganglia, and thus became ineffective In retrospect, I think this represented only half the truth, applying chiefly where the spine itself was involved In most cancer cases the neurones seem to have a variable and lesser resistance to phenol action Whether this is caused by preliminary inflammatory change and infiltration by round cells or inclusion bodies, I cannot say, but it makes some difference in the reaction following intrathecal phenol injections The impact is conversely more severe with non-malignant conditions, and the hazard is greater in the presence of scoliosis and arthritis or where the limb is already impaired from disease or previous operation

I have been making a further approach recently towards more accurate placing and dosage of phenol solutions for cancer cases, which may afford a helpful indication for safer injection in non-malignant conditions

First, pain areas are fully mapped out on standard diagrams of nerve segments[2 3] Five days after injection, these areas are remapped and further appropriate injections are made until pain is totally eradicated The segmental diagrams referred to are invaluable for this purpose, and I wish to acknowledge the help I have received from them

Secondly, an early indication of sensory effects is ensured by good backward rotation of the patient (as in fig 3B of my 1955 paper)[4] *For below* D12 *level, 1 ml of phenol (1 in 20 in* glycerin) is the arbitrary upper limit for safe dosage. Half this amount (i e., 0 5 ml) is injected, followed by immediate slight elevation of the patient for a second or two to move the solution on After a few moments, paræsthesiæ may begin, if they are severe or associated with cramps, for the second half of the injection less than 0 5 ml is given Skin sensation should be tested after the preliminary 0 5 ml If there is anæsthesia, the second part of the injection should be delayed until it has cleared and should be reduced below 0 5 ml

Differences in analgesia between the injected side and the opposite side give a valuable indication of where the agent is flowing and of whether further tilting is necessary in either direction

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[2] Brain, W R Diseases of the Nervous System, pp 30, 31 London, 1955

[3] Purves-Stewart, J, Worster-Drought, C. Diagnosis of Nervous Diseases, p 80 London 1952

[4] Maher, R. M *Lancet*, 1955, i, 18

The same technique, using two doses, each of 0 5 ml , is applied with the silver nitrate agent (1 ml of phenol 1 in 25, containing silver nitrate gr $^{1}/_{30}$ per ml) but this agent is never used for non-cancerous conditions, or above lumbar level Glycerin is used as the conveyor at the lumbar level since it does not tend to spread or to clog up roots for later injections

For *non-malignant* conditions, I have been recently using 0 5 ml of phenol, 1 in 20 in glycerin, at one session intrathecally At a later date, a similar injection of 0 5 ml can be given at another interspace if needed

Dr Lehoczky (March 8) again refers to the aqueous solution of phenol employed at the 1st or 2nd sacral foramen, which I always use instead of intrathecal injection for sciatic pain of non-malignant origin Since 1952 I have also used it frequently for sciatic pain of malignant disease, in one form or another Sometimes it is completely successful, but where it fails, the intrathecal method is more powerful Furthermore, transsacral methods cannot effectively reach higher segments for malignant disease It seems that each method has its own particular sphere of usefulness

The application of intrathecal methods is essentially for cancer, with a very limited and cautious approach for pain of non-malignant origin at the present time

Rochdale R M MAHER

NEW METHOD OF PHENOBARBITONE ADMINISTRATION

SIR,—May I briefly reply to Dr Penman (March 29) ?

1 " No conclusion whatever can be drawn from the data presented "—The facts are that each and all of the 18 patients showed a striking improvement, both in respect of personality and mental state, and also in the frequency and severity of their epileptic convulsions, whether or not they were receiving other drugs

2 " There can be no guarantee that the patients took their various anticonvulsants as regularly before the spansule period as they did during it "—For many years a rigid routine and discipline has been in force in this hospital whereby the epileptic patients are lined up regularly at the prescribed times of day, and the medication is administered in the presence of the nurse The same nurses had in fact been attending the 18 patients concerned for a number of years before the new method of treatment was adopted

3 " Much or all of the ' improvement in personality ' may have been due to added interest shown in the patients during this stimulating trial "—There had, prior to my " interest ", been no lack of stimulation in this respect, and on two occasions previously individual doctors, by their work with these particular cases, had in fact produced slight but temporary improvement both in the mental state and in the convulsions But they had not been able to achieve the definite and gradual reduction of convulsions, with final elimination, nor the striking improvement in the mental state and personality, which has resulted from the new method of therapy If such an " interest " is so important and valuable in the treatment of epilepsy, there should be a great future for psychotherapy in this condition, but few doctors who have had experience in the management of epileptics would agree that it is likely to have much success

4 " Since fits occur especially at times of bodily inactivity and mental vacuity, this added interest and stimulation may have helped to reduce their frequency "—Surely, the absence in the body (for approximately twelve hours, at night) of a sufficient supply of anticonvulsant medication is a more probable reason for convulsions The presence of an adequate supply of such medication throughout the twenty-four hours must give the maximum protection and help to the patient, as regards both disturbance of sleep and abnormal electrical activity within the nerve-cell Maintained control of both these important factors has been achieved since the introduction of ' Spansule ' therapy, in each and every one of the 18 epileptics treated Previously there had been many disturbances from fits and temper tantrums at night

5 " Credit for improvement cannot be assigned to any one of those drugs separately "—Much credit must be given to spansule phenobarbitone for the phenomenal improvements obtained in my patients after it was adopted If these improvements cannot be attributed to spansule, either wholly or in part, then they *must* be due to the drugs the patients were already receiving If these drugs, combined with " interest " and psychotherapy, were really so effective, many epileptics now in colonies and mental hospitals could have remained in society without danger to themselves or others

6 " Eighteen is too small a number of cases "—Dr Penman is, I am sure, aware that improvements such as I have reported can be proven to be significant and statistically valid with 18 patients or even fewer The advisability or otherwise of controlled trials, using inert substances, in patients with epileptic convulsions is open to discussion

7 " Dr O'Connor's results are striking indeed, but others hardly less striking have been overthrown by controlled trials, good examples being those of Kurtzke and Berlin and Booth et al "—Dr Penman's original contention that " *no conclusion whatever* " can be drawn, would seem to conflict somewhat with his closing remark, " Dr O'Connor's results are striking indeed " The fact that the trials to which he refers were both concerned with multiple sclerosis, and bore no relation to epilepsy with its specific complexities, makes his " good examples " appear weak and irrelevant

Warley Hospital,
Brentwood, Essex DESMOND C J O'CONNOR

SEQUELÆ OF INTRA-ARTERIAL INJECTION OF THIOPENTONE

SIR,—We are interested in the sequelæ of inadvertent intra-arterial injection of thiopentone Gangrene has been reported after the use of 10%, and in a few cases of 5% solutions, but we can find no such complication reported after the 2 5% solution now in common use

We should be grateful if any of your readers could supply us with information, which will be naturally treated confidentially, of intra-arterial injection, or of cases where venous thrombosis occurred, when either 2 5% or 5% has been used

Nuffield Department of Anæsthetics,
Radcliffe Infirmary, Oxford D L PRYER

PSYCHOSIS AND TREMOR DUE TO MECAMYLAMINE

SIR,—I was interested in the article by Dr Harington and Dr Kincaid-Smith (March 8), as I have had a similar case where mecamylamine was not given

A man, aged 60, had been known to have hypertension since May 18, 1955 He had had several attacks of congestive cardiac failure precipitated by an erratic consumption of digitalis He was admitted to the Addington Hospital on May 22, 1956, for an intercurrent *salmonella* infection He also complained of weakness, giddiness, and dyspnœa on effort His blood-pressure (B P) was 220/120 mm Hg There was no papillœdema, no renal dysfunction, and no anomaly of the central nervous system The heart was enlarged but there was no failure then The B P was controlled by reserpine 0 25 mg t d s and pentolinium 200 mg t d s He was discharged on May 23, 1956

Within a month the B P had risen again to 230/145, and the dosage of pentolinium was increased to 200 mg q i d After this the B P remained at levels varying from 160/105 to 180/120 for four months

On Sept 5, 1956, he complained of loss of weight and increasing depression On examination he was found to be heavily pigmented (more than his usual pronounced sunburn) and the mucosæ had a bluish tint There was a coarse tremor of all limbs, with a high muscle tone The reflexes were brisk, power normal, plantars flexor B P 180/100 Reserpine was discontinued because of the depression.

Two weeks later he was readmitted. The tremor was less obvious but the rigidity still present. His depression had deepened further and he was complaining of frequent involuntary seminal emission. The B.P. was 190/120. Lumbar puncture produced a normal fluid. The urine showed a trace of albumin and occasional red blood-cells. The blood-urea was 48 mg. per 100 ml.

Pentolinium was replaced by hexamethonium for two days, but then recommenced. The patient discharged himself after three days and had no more antihypertensive treatment.

A month later he was readmitted because of severe psychosis. He was disorientated and hallucinated, and showed paranoid tendencies. His speech was slurred but muscle tone was normal and the tremor very slight; B.P. 270/160. The urine contained a trace of albumin. The blood-urea was 27 mg. per 100 ml. The hospital psychiatrist diagnosed an organic type of psychosis due to cerebral arteriopathy associated with hypertension and suggested certification. The patient, however, absconded before this could be done and has not been seen since.

This case seems to be very similar to the cases mentioned by Dr Harington and Dr Kincaid-Smith, but this patient has at no time had treatment with mecamylamine. This would suggest that the symptom-complex may be due to hypertension per se or to its treatment with any ganglion-blocking agent.

Addington Hospital,
Durban
W. HIFT

INFANTILE GASTROENTERITIS

SIR,—Dr Librach has incurred much criticism for venturing to doubt if strains of *Escherichia coli* are of major importance in the ætiology of infantile gastroenteritis. During 1957 I admitted to hospital 38 cases of gastroenteritis in infants under two years. In all cases fæces were cultured, but *Esch. coli* of the presumed pathogenic types was isolated in only 3 instances. These included none of the 5 infants who were gravely ill. I have had similar experience in previous years.

Until the association can be more generally and constantly demonstrated, we should be permitted to keep an open mind on this matter. Incidentally, about ten years ago, proteus was frequently suggested as an important organism in this connection, a belief which now seems to be discarded.

Croydon
J. J. LINEHAN

PATIENTS FROM ABROAD

SIR,—I write as a practising surgeon in Beirut, Lebanon, who for 15 years has worked with a British surgeon specialist and has admired British medical skill and practice both at home and abroad.

Recently a colleague of mine heard that I was contemplating a voyage to England and asked my help in escorting one of his patients. This patient had been booked in a private nursing-home as a paying patient. Confirmation had been received that a bed would be available for the required period. On applying for a visa, we were informed that she could not be granted entry without permission from the United Kingdom. This, we were told, was to protect the British taxpayer. A reply-paid telegram was sent, but two weeks later we were still awaiting the answer.

If this patient is being admitted to a private nursing-home, and is therefore a paying patient, where is the risk to the British taxpayer or to the N.H.S.? If there were any danger of her being financially insecure, who would be more likely to know about it—the authorities in England, or the consular representative on the spot? Surely the foreigners seeking to benefit from British medical skill and progress and willing to pay for it should be encouraged to do so, and facilities should be given for their quick admission to the United Kingdom.

Beirut, Lebanon.
I. AYOUB

*** Dr Ayoub informs us that a visa was in fact granted for the entry of the patient into the United Kingdom, but arrangements had already been made for her to receive treatment in Switzerland, where she now is.—ED. L.

INTERMITTENT HYPERPARATHYROIDISM

SIR,—Dr Whitby (April 26) reports a case of hyperparathyroidism due to an adenoma which he claims was intermittently overactive; this claim carries considerable physiological implications. In fact, some of the findings are hard to reconcile with the idea of intermittent overactivity. Parathyroidectomy, which did not induce a hypoparathyroid state, halved the 24-hour output of calcium in the urine, whereas before operation no variations of similar extent occurred; the variations that did occur before operation seemed unconnected with changes of the serum-calcium level.

In proven cases of primary hyperparathyroidism, the serum-calcium level can be found to be within normal limits at times, and abnormal at other times, in one and the same patient; this emerges clearly from fig. 48 of Albright and Reifenstein,[1] and my own experience supports this.

A considerable experience of determining the 24-hour output of calcium in the urine of outpatients suffering from stone in the urinary tract has shown me that, when taking their customary diets, outputs of up to 350 mg. of calcium a day must be accounted as normal. This agrees with Pyrah's findings.[2]

Sheffield.
ARTHUR JORDAN

BUDGERIGARS AND POLIOMYELITIS

SIR,—This interesting correspondence raises some points on which I should like to comment, as the result of experience of avian diseases in the field and in the laboratory. It also clearly shows the need for closer cooperation between the medical and veterinary professions.

Leg weakness is a common symptom in ailing budgerigars, canaries, and other small birds, and if they are not handled and examined it can easily be confused with paralysis. In budgerigars the symptom is often associated with severe enteritis of unknown ætiology, which is very common in this species. Some specific diseases affecting cage birds also produce the symptom of leg weakness.

True paralysis, however, does occasionally occur in these species, and, apart from trauma, probably the commonest cause in budgerigars is the pressure exerted by renal neoplasms on one or both sciatic nerves, which in birds are in close contact with the kidneys.

It is also thought that certain vitamin deficiencies may cause paralysis in some species of cage birds.

Even if there is doubt that budgerigars may contract infectious poliomyelitis, it is well known that cage birds are occasionally infected with other diseases to which man is susceptible. The best example of course is psittacosis (ornithosis) which infects numerous species of birds and is commonest in this country in pigeons and recently imported psittacines such as parrots and parrakeets. A more common disease, however, is salmonellosis, usually caused by *Salmonella typhimurium*, which affects numerous species, including budgerigars and canaries.

Another disease (common in pigs and turkeys) affecting budgerigars and some species of finches is that caused by *Erysipelothrix rhusiopathiae*, which is transmissible to man, causing erysipeloid.

Ministry of Agriculture, Fisheries and Food,
Central Veterinary Laboratory,
Weybridge, Surrey
I. F. KEYMER

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[1] The Parathyroid Glands and Metabolic Bone Disease. Baltimore, 1948.

[2] *Proc. R. Soc. Med.* 1956, 49, [illegible]

TESTING OF STERILISATION METHODS

SIR,—Dr Schwabacher, Dr Salsbury, and Dr Bailey (April 19) wisely advise against the use of the present "sterility test packets" They also affirm that Browne's steriliser control tubes are reliable This is certainly true if these tubes are correctly stored (at 70°F or less) Thus far Dr Schwabacher and her colleagues confirm conclusions reached by others[1-4]

It surprises me that they did not refer to Dr J C Kelsey's recent paper,[3] which clearly shows that unpredictable variables may complicate the testing of sterilisers with any organisms, but particularly with *Bacillus subtilis* and similar mesophilic spore-bearers The modifications of current procedure proposed by Dr Schwabacher and her colleagues seem to me only to add new complications Having read Dr Kelsey's paper and having had some experience of testing sterilisers with both mesophils and thermophils, I agree with him that organisms should be used to test sterilisers only for special purposes, and that for routine tests a chemical indicator is the most useful

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J W HOWIE

RECORDS OF IMMUNISATION

SIR,—With the increasing amount of prophylactic immunisation, is it not time that something be done on a national basis to issue permanent records to all those receiving these injections? At present any person may have been actively immunised against any or all of at least five diseases (smallpox, diphtheria, tetanus, pertussis, and poliomyelitis) International vaccination certificates are already in force against smallpox, yellow fever, and cholera

It is rare for patients or their relatives, attending hospital casualty or other departments, to have the remotest idea whether or not they have been immunised against, say, tetanus, certainly they can never remember when it was done, and moreover they cannot be expected to appreciate the significance of the date of the test boosting injection

Parish[5] writes

> "Accurate record-keeping is essential, and should include the dates of inoculation, the correct name of the preparations, the batch numbers, the dosage administered, and reactions (local, general, etc) Every child should have a personal immunisation card which should be made out at birth and filed with the utmost care It must be readily available when inoculations of all types are given, or when the child contracts an infectious disease Intelligent parents could surely be trusted to safeguard duplicate cards, while the local authority remains responsible for the original The free movement of populations which takes place in modern times makes duplication of these records essential"

There are clearly many problems (records will be lost, and so on), but surely they are not insuperable

In many ways it is a pity that the wartime identity cards were abandoned they could have been modified to include information about blood-group and immunisations As far as immunisations are concerned a system of coloured inserts (each denoting a different course of injections), as used by the National Blood Transfusion Service for blood-donors, would go some of the way towards overcoming the problem of lost records Most people can remember the colour of their blood-group card even if they have lost it

It has been suggested that tattooing could be used for permanent recording, but the multiplicity of information required makes this impracticable, and neither children nor parents could be expected to agree to the procedure

Perry and Parish[6] suggested the use of a consistent set of abbreviated titles for all immunising substances, to ensure speedy, accurate, and unambiguous recording The first part of the abbreviation is the shortened name of the disease, if only one disease is named in the title, the abbreviation is three-lettered, (e g , Dip=diphtheria, Tet=tetanus), the only exception is that typhoid and typhus should be written *in full* to avoid confusion When protection is to be conferred against more than one disease, the abbreviations for their names are the initial letters—e g , TABT=typhoid, paratyphoid A and B, and tetanus

The second part of the abbreviation, which is separated from the first part by an oblique stroke, is either Vac (indicating any substance for *active* immunisation) or Ser (any form of serum for *passive* immunisation) There is again one exception, since both a toxoid and a vaccine are used for active immunisation against the staphylococcus, Tox is used for toxoid

The possibility of international adoption explains the preference for "Vac" instead of "Pro"

When necessary, the particular type of product may be specified in a third part of the abbreviation, again separated by an oblique stroke—e g , Dip/Vac/APT for diphtheria, alum precipitated toxoid

In this hospital, we are now actively immunising those who have had a general reaction to a test dose of tetanus antitoxin, and shortly intend to offer a course of toxoid to anybody that has had this antitoxin, so the problem of these records is considerable If there is enough support from others even more concerned than we who are working in hospitals, surely the Ministry of Health could be persuaded to take action on this very important problem

Orpington Hospital,
Orpington, Kent

KEITH J RANDALL

FREQUENCY OF THE TRUE (CHROMATIN-POSITIVE) KLINEFELTER'S SYNDROME

SIR,—The frequency of the true or chromatin-positive Klinefelter's syndrome has been estimated as 1 in 10,000 males[7] Our findings suggest a frequency as high as 1 in 1000

As the syndrome is probably often associated with mild mental deficiency,[8, 9] we examined the chromosomal sex by buccal smears of every second boy of the 671, aged 7 to 15 years, who attend the special State school for children with mild mental deficiency (I Q is in general between 75 and 85) in Zürich Of the 336 boys examined, 8 have been found to be chromatin-positive An independent observer (Prof H R Wiedemann in Krefeld, Germany) studied the blood-smears of these 8 boys and confirmed our results 6 of these boys are aged 12 years or younger and 2 are 13 or older All have normal male external genitalia The younger 6 show no signs of puberty and no gynæcomastia The older 2 have pubic hair, gynæcomastia, very small testes in view of their puberal development, and increased gonadotrophin excretion In the younger 6 no hormone studies were done Testicular biopsy was done in only 1 of the younger boys, it showed no tubular sclerosis and absence of Leydig cells, which is normal at this age[10] A detailed report about all 8 boys will be published later According to common views these boys must all be regarded as

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[7] Lennox B Ferguson-Smith, M A, Mack W S, Stewart, J S S Symposium on Nuclear Sex 1958 (in the press)
[8] Zublin, W *Acta endocr, Copenhagen* 1955, 14, 137
[9] Pasqualini, R Q, Vidal G, Bur, G E *Lancet*, 1957, ii, 164
[10] Siebenmann, R E, Prader, A *in preparation*

examples of true (chromatin-positive) Klinefelter's syndrome (with a remote possibility of true hermaphroditism)

As we found 8 cases in half of the 671 boys with mild mental deficiency, the estimated number with Klinefelter's syndrome in the whole group is 16 The number of boys of the same age-group in the same city is 19,965 This means that the frequency of true Klinefelter's syndrome among boys with mild mental deficiency is 1 in 42, and among all boys at least 1 in 1248 As we know several other patients with Klinefelter's syndrome in the same city, who were intelligent enough to pass the normal school, the frequency among all males must in fact be higher, probably about 1 in 1000

A PRADER
J SCHNEIDER
J M FRANCES
W ZUBLIN

University Children's Hospital,
Zürich, Switzerland

NEOPLASIA

SIR,—May I, as a speaker on endogenous cancer at the conference on Neoplasia, reported in your issue of April 19, emend some impressions which it was not my intention to convey?

Discussion of old theories of cancer—for example, that senescence *might* be a cause—does not imply agreement Cells of young children are liable to malignant change as we know from the occurrence of embryomas, and fœtal cells grafted together with carcinogenic chemicals readily become cancerous

Although it is possible to induce cancer by subcutaneous or topical application of various chemical compounds, some even of endogenous origin, this does not exclude the possibility that the vast number of sporadic tumours are *not* caused by similar conditions in nature Inbred strains of animals, in which spontaneous tumour incidence is often greatly increased, provide material for testing other ideas But I would not myself postulate anything as vague as a cell "irritant"

Royal Beatson Memorial Hospital,
Glasgow

B D PULLINGER

TOXÆMIA OF PREGNANCY

SIR,—The continuing attempts to incriminate aldosterone in the ætiology of pre-eclampsia, in view of all the evidence denying it a share, merely reveals hypothetical ingenuity without plausibility

Unless it can be shown that salt restriction in the diet *enhances* the toxæmic process the following data further deny aldosterone a part in the production of pre-eclampsia

Orti et al [1] have proved the presence of an aldosterone-stimulating substance in the urine of adrenalectomised rats deprived of salt, by injecting their urine into intact hydrated rats in which it caused a *decreased* excretion of salt Quite obviously this substance in the urine of the adrenalectomised rats deprived of salt could not have been aldosterone, although it provoked the secretion of aldosterone when injected into the intact and hydrated subject

It seems therefore that depriving an animal of salt indirectly provokes aldosterone secretion All such deprivation would therefore conduce to salt retention and *if in significant amounts* to toxæmia—which is not a clinical experience This evidence further denies aldosterone ætiological significance

London W 1

JOHN SOPHIAN

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[1] Orti, E., Ralli, E P., Laken, B , Dumm, M E *Amer J Physiol* 1957, 191, 323

CLINICAL GERIATRICS

SIR,—The replies of Dr Agate and Dr Howell (April 5) to my query, arising from Dr Howell's original letter, as to what exactly constitutes "clinical instruction in geriatrics", are largely irrelevant.

Dr Agate's statement, "Elderly people with pneumonia *seldom exhibit any pyrexia*", is surely an exaggeration if the word "seldom" means what it usually does That delirium is fairly common in elderly patients with infections has been known for centuries, and has, surely, been taught in teaching hospitals for many years That infarction is frequently silent in people over 70 is possibly true, but the word "frequently" is surely hyperbole. Is occlusion "silent" more commonly in those in the seventies than in those in their sixties? Moreover, does such incidence refer to first attacks? These are very important points Dr Agate's description of geriatrics as "hard work in the clinical field" is an imaginative metaphor, but exactly what does it imply?

Dr Howell queries my citation of 68 for the age of my hypothetical patient To him, apparently, geriatrics starts at 80 Is there any official view as to what constitutes geriatrics? I should have thought that the age when a person is legally entitled to an old-age pension would be the only acceptable definition But, on the other hand, I remember an international conference on geriatrics held in London when several American physicians included *in their series of patients* some even below the age of 50 Is not all this classification of diseases according to age very artificial?

London, W 1

M H PAPPWORTH

ORGANISMS IN THE RESPIRATORY TRACT DURING ACUTE RESPIRATORY INFECTIONS

SIR,—The excellent contributions by Dr Brumfitt and his colleagues [1] and by Dr Steiner and his colleagues (March 22) prompt me to refer to the importance and value, from a diagnostic point of view, of the presence of specific antibodies in bronchial mucin

In 1918, I investigated the exudate of dysentery stools for agglutinating antibodies to the dysentery group of organisms,[2] and found that specific agglutinins were present in diagnostic amounts at an early stage of infection

Since then, investigations have been carried out by several workers (their findings have been summarised by Morgan et al [3]) on the presence of local antibodies in the mucus derived from the intestine and reproductive tract and from the bronchi [4-8]

If sputum, to which has been added a small volume of saline solution, is subjected to mechanical shaking with glass beads and centrifuged, the supernatant fluid can be investigated for its antibody agglutinin content against stock suspensions or against suspensions of selected colonies from plate cultures These tests are much facilitated by use of the Garrow agglutinometer slab method [9,10]

In this way bacterial flora of the mouth and pharynx (which do not produce antibodies) can be excluded and the necessity of obtaining material from bronchi by direct aspiration and swabbing becomes unnecessary

West Worthing, Sussex

ARTHUR DAVIES

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[1] Brumfitt, W , Willoughby, M L N , Bromley, L L *Lancet*, 1957, ii, 1306

[2] Davies, A. *ibid* 1922, ii, 1009

[3] Morgan, W T J , Pierce, A E , Smith, H. *Proc. R Soc Med* 1953, 46, 783

[4] Francis, T *Science*, 1940, 91, 198

[5] Francis, T *ibid* 1943, 97, 229

[6] Fazekas de St. Groth, S , Donnelley, M *Aust J exp Biol med Sci* 1950, 28, 45, 61

[7] Fazekas de St. Groth, S *ibid* 1951, 29, 339

[8] Fazekas de St. Groth, S , Donnelley, M, Graham, D M *ibid* 1951, 29, 323

[9] Garrow, R. P *Lancet*, 1917, i, 262.

[10] Manson-Bahr, P Manson's Tropical Diseases, p 952. London, 1935

THE Y CHROMOSOME IN MAN

SIR,—In collaboration with Mr Peter Dickinson I have recently investigated a case which appears to illuminate the function of the Y chromosome in man

The details, briefly, are that, in the course of an operation for left inguinal hernia, a man was found to have, in the hernia, a uterus and uterine tubes and a right undescended testis The left testis was in the scrotum The penis and scrotum were quite normal No ovarian tissue was found The oral mucosa and neutrophil nuclear morphology were chromatin negative The histology of the left testis is exactly that of chromatin-positive cases of Klinefelter's syndrome as described by Ferguson Smith et al[1] and that of a chromatin-positive case of true hermaphroditism published by Armstrong et al[2] except for the absence of Barr's chromatin mass The right testis displays an identical picture as far as the seminiferous tubules are concerned, but the clumps of interstitial cells are atypical

The coincidence of an identical type of tubular atrophy and hyalinisation in chromatin-positive Klinefelter's syndrome and true hermaphroditism and in this chromatin-negative case suggests

(1) That the testicular changes in the two former are due not to the presence of two X chromosomes but to the absence of the Y chromosome The presence of the testis is another matter

(2) That our patient, who has not two X chromosomes, has probably no Y chromosome

(3) The presence of uterus and tubes, and perhaps the atypical interstitial cells in the right testis, in our case, indicates that Y contains a gene which is antagonistic to the X feminising genes and plays a part with autosomal masculinising genes in the normal X, XX switch mechanism

I postulate the existence of two genes on the Y chromosome (1) a gene necessary for normal development and maintenance of the seminiferous tubules of the testis (perhaps it is necessary for normal hormone production by the interstitial cells), and (2) a male determining gene

A full account of the case is being prepared for publication

I wish to thank Dr Bernard Lennox, of the Western Infirmary, Glasgow, who has seen sections of the testes, and Dr C N Armstrong, of the Royal Victoria Infirmary, Newcastle, who has been very helpful in hammering out the theoretical implications of the case

Department of Anatomy,
The Medical School, King's College,
Newcastle upon Tyne

JOHN GRAY

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[1] Ferguson Smith, M A, Lennox, B, Mack, W S, Stewart, J S S *Lancet*, 1957, ii, 167

[2] Armstrong, C N, Gray, J H, Race, R R, Thompson, R B *Brit med J* 1957, ii, 605

Parliament

Too Many Prisoners

Mr Butler's speech a year ago in the House of Commons raised high hopes for the reform of our prisons, the debate in the House of Lords on April 23 showed how seriously progress is being hindered by the alarming rise in the prison population In opening the debate Lord PAKENHAM pointed out that since Mr Butler spoke the number of prisoners had risen from 21,600 to 24,309 As a result overcrowding was worse, and whereas in 1957 only 2000 men (and that was 2000 too many) were sleeping three in a cell, the number today was 4389 Nor was immediate relief likely, for the increase in the Borstal population had forced the authorities to use the first new prison to be built this century as an extra Borstal institution In view of the acute shortage of accommodation it was lamentable to find that in the estimates for 1958–59 the provision for new buildings and alterations (as apart from repairs) was down by £16,000 Given such prison accommodation and the present wave of crime, he suggested that it was important to keep down the number of people in prison The Maintenance Order Bill would do something to reduce the number of civil prisoners and he would also like to see an increased use of adult probation, more treatment outside prison for sexual offenders, the development of attendance centres, and the extension of a parole system

Turning to the important and neglected question of research, he agreed that this was probably better conducted outside Government departments But if the Government did not largely pay for it there were no signs of anyone else doing so In 1957–58 £3000 was allocated to research, in the estimates for 1958–59 the figure was £11,000 which though better was still derisive Excellent officials in the Home Office were showing a good deal of initiative in promoting projects, but clearly it had all to be on a pretty small shoestring Without an institute of criminology research would remain uncoordinated

He was glad that recruitment to the prison service had improved, and the number of officers had risen from 3636 in 1957 to 4093 today But this improvement, too, had been partly nullified by the increase in the number of prisoners The hours of work in central prisons were 30–42 a week, but in local prisons the average was only about 25 Though some good things had been done Lord Pakenham feared that our prison services were still "last in the queue" of the social services, and if present trends continued, they would soon need a telescope to keep their colleagues in sight

Lord MANCROFT admitted candidly that the Home Office's plans had been sadly affected by the present financial stringency and by the substantial and unwelcome rise in the prison population The total population of our prisons and Borstals was 24,500 at the end of March this year—the highest figure yet recorded The high proportion of this increase among young men was especially alarming, the Borstal population had risen from 2600 in 1956 to 4000 These young offenders were the early arrivals of the post-war bulge in the birthrate If this level of crime was carried forward into the full effects of the bulge, the situation in a few years' time would be appalling, and we might well expect a Borstal population of over 5000 But he hoped that this phenomenon would pass with the generation born just before or in the early days of the war

He agreed that the problem could only be tackled by increasing accommodation and reducing the numbers of prisoners and some progress had been made

It was hoped to establish an experimental attendance centre for men of 17 to 21 years at Manchester this year A second junior detention centre had been opened for 65 boys and a Borstal for 50 girls The new security prison was expected to be ready in June, but he regretted that it must begin its career as a Borstal A second new prison should be completed in 1960, and the new psychiatric prison in 1961, a new central Borstal reception centre in 1960, a girls' security Borstal in 1960, and a boys' in 1961 To meet the immediate need a Ministry of Supply hostel had been acquired as an open prison for 480 men

Research was of course fundamental to any consideration of the causes or treatment of crime, and last year the Home Secretary had set up a research unit within the Home Office itself Increased support had also been given to projects at universities and other institutions

Lord Mancroft pointed out that one of the greatest obstacles to prison reform was the inheritance of a large number of unsuitable but solidly constructed prisons, and it would be unrealistic to make any plans on the assumption that they could be replaced by modern establishments in the near future Overcrowding had hindered the Commissioners' plans for modernisation and conversion as it was no longer possible to clear space to allow the work to proceed But some improvements, notably in sanitation, had been achieved

Central bath houses had been completed at 7 prisons and improvements would be undertaken this year at 3 more A pilot scheme for modernisation of sanitary accommodation in wings, workshops, and exercise yards at Wormwood Scrubs should be completed next year, a similar programme had been started at Dartmoor, and a programme for gradually modernising sanitary accommodation in all prisons would begin next year

Speaking in the debate Lord ASTOR suggested that the prisons were in much the same position as the hospitals They had a sensible wise direction at the top, a devoted but overworked staff, and obsolete overcrowded buildings It was expensive to keep a person either as a prisoner or a patient, and it was therefore important that only the right people should go to prison, as it was important that only the right people should go to hospital

Continuing his simile he said that prisons were like hospitals where the patients had been sent by doctors who had had no specialist training, who had not had the benefits of laboratory tests on the nature of the disease, who all too often never visited the hospitals, who merely prescribed the amount of medicine the patient was to receive with little expert knowledge of its chemical contents, and whose future had little to do with the percentage of patients successfully treated If we ran our hospitals on those lines what a chaos there would be

But that was what happened in our prisons Our judges, our magistrates, and our recorders had no real training in penology Was it not extraordinary that no Law Lord had taken part in this debate? Lord Astor thought that this abstention showed the extraordinary detachment of judges towards prisons With the work of Freud we had had a real break-through in the study of mental health—a new and exciting chapter in the knowledge of how the human mind worked, what made people go wrong, and how treatment was likely to affect them As a cockshy, Lord Astor threw out the suggestion that the education of barristers should be extended to include, at some period in their career, a study of psychology and penology and some form of practical work such as prison visiting or probation-officer work Greatly daring he went on to suggest " refresher courses " for magistrates and even judges

Supplies of Morphine for Port Medical Centres

On the adjournment on April 24 Mr JAMES CALLAGHAN drew attention to the fact that though 24 of our largest ports had medical centres, staffed with qualified nursing sisters, which handled about 230,000 accidents a year they were not allowed to keep supplies of morphine for use in emergencies The National Dock Board had applied to the Home Office in 1950 and in 1953 but had twice been refused permission. Mr Callaghan described a distressing accident in Cardiff docks in October when a man's leg was torn off his body Though three State-registered nurses were in attendance the man had to be brought ashore and travel in an ambulance over 3 miles of bumpy dock road to a hospital before he received an injection of morphine

Mr DAVID RENTON, joint under-secretary of State for the Home Department, said that it must not be overlooked that, though morphine did good by alleviating pain, it did harm by masking symptoms which might be important in diagnosis This was one reason why it had been generally accepted by the medical profession that wherever possible a doctor should be present when morphine was administered Another reason for caution was that this country was comparatively free from drug addiction, and the reason was the strictness and efficiency of our system of control That system was based on the general principle that nobody should be in possession of a dangerous drug unless authorised by the law Our dangerous drugs legislation gave effect to international conventions which this country had ratified and which required the exercise of stringent control over the supply, possession, and use of dangerous drugs Within the framework of the legislation, however, special arrangements had been made for the administration of morphine in particular cases Generally, these special arrangements related to circumstances where accidents happened and where it would be impracticable or unreasonable to insist on the presence of a doctor for the administration of the drug Thus special authority had been given to certain first-aid men in the mines and to mountain rescue parties Docks varied a good deal as to their proximity to the nearest town or hospital from which doctors could be summoned At the moment there was no evidence that the circumstances of docks in general justified a broad exception to the general principle, but he was arranging for the matter to be urgently considered, first in relation to Cardiff docks in particular In making these inquiries the Home Office would give the fullest weight to humanitarian considerations and the desire of all to minimise suffering

QUESTION TIME

Russian Vaccine for Multiple Sclerosis

Dr DONALD JOHNSON asked the Minister of Health, as representing the Lord President of the Council, whether he would consult the Medical Research Council with a view to obtaining a supply of the Russian vaccine for multiple sclerosis for the purpose of conducting, in this country, suitable tests of the efficacy of this vaccine —Mr DEREK WALKER-SMITH replied No final decision can be taken about the use of this vaccine until information about it is received from the Soviet Union. In the meantime, in view of the evidence available from laboratory investigations carried out in the United Kingdom and in America which throw doubt on both its safety and effectiveness, the Medical Research Council does not propose to undertake clinical trials of its possible value in the treatment of multiple sclerosis Dr JOHNSON May I ask whether the Minister recalls that he also said that he will allow imports of this vaccine through private sources, and that people who are extremely anxious to effect such imports—if the vaccine is any good—are desperately in need of further guidance on the subject?—Mr WALKER-SMITH The imports are on the individual guidance and responsibility of a practitioner recommending it. The tests on this subject will take a long time to carry out. Meanwhile, pending information from the Soviet Union, my hon friend may be interested, for example, to look at the conclusions of Professor Dick, published in the *British Medical Journal* earlier this year, and he will also be able, I hope, to study the conclusions of Dr Sabin of Cincinatti when they are published

Dr EDITH SUMMERSKILL In view of the fact that we have little information about the ætiology or the treatment of this disease, can the Minister tell the House why, because there has been little success on the part of those concerned with the two inquiries, the Medical Research Council should not examine this vaccine, even though it does take a long time?—Mr WALKER-SMITH There is no evidence that any adequately controlled clinical trial of the effectiveness of this vaccine has ever been undertaken anywhere In a disease of such protracted course over many years in which all patients show periods of remission which may be complete for several years, the design and execution of a therapeutic trial is exceedingly difficult. However carefully planned any such trial may be, I am advised that it cannot be expected to provide reliable results in less than five years, and perhaps we had better await the Soviet answer

Mrs BESSIE BRADDOCK In view of the fact that the Minister is prepared to allow the import of this vaccine privately, does he not think it would be advisable for some investigation to take place? If perchance through a private experiment a sufferer got great relief, it might cause a difficult situation if this vaccine could be obtained only through private sources — Mr WALKER-SMITH The position is that I would not stop the import of this vaccine if it were undertaken on the individual responsibility of a general practitioner who took responsibility for his own judgment. But in the generality, from what I know and have so far been able to ascertain about it, I could not recommend it, pending further investigation, particularly in view of the conclusions, not only of Professor Dick or Dr Sabin to whom I have referred, but also of Dr Broman of Gotenburg

Poliomyelitis Vaccine

In answer to questions about the supply of poliomyelitis vaccine Mr WALKER-SMITH said Batches of vaccine from the two British manufacturers which were distributed to local health authorities last week total over $^1/_2$ million doses, and a batch of Canadian Salk vaccine of $^{1}/_{2}$ million doses will be distributed within the next few days Over $8^{1}/_{2}$ million doses of vaccine will then have been distributed in Great Britain since the start of the scheme, $4^{1}/_{2}$ million of them since the beginning of this year Further vaccine should be distributed next month These supplies will enable local health authorities to make good progress with vaccinations

In addition to what is already in the pipeline, I am arranging for the purchase of a further quantity of American Salk vaccine in addition to the 7800 litres and replacements previously ordered from Canada and the U S A

Mr Barnett Janner Does the Minister recollect that many months ago he was asked why he was not purchasing adequate quantities of vaccine from North America? Is it not a fact that had he ordered the requisite quantity and made allowance for a breakdown, he would be in a position today to meet all the requirements, as America then had supplies and was able to supply him? Is the Minister also aware that much of the vaccine that has been produced in America has been sold in America, and that he has been scandalously negligent in not providing what is necessary for this country?—Mr Walker-Smith When the original imports of Salk vaccine were arranged the Government were acting under the advice of the Medical Research Council that the imports should be regarded as a temporary measure until adequate supplies of British vaccine became available There was no reason at that time to foresee the interruption of British supplies on the scale which has unfortunately happened, because they had been coming forward regularly for some time before that date The stocking of Salk vaccine at that stage would have been inappropriate because it was not possible to make an estimate of the acceptability of Salk vaccine at that stage, having regard to the right of rejection The hon Gentleman has left out of account in his suggestion the consideration that the potency of this vaccine is not permanent It is a perishable commodity

Dr Summerskill As the Minister knows, the number of people eligible for inoculation is 10 million, and 50% of them have registered That means that there will be 10 million inoculations to be given if they are all to have 2 inoculations Can he say whether before June—that is before the time when poliomyelitis rears its very ugly head in this country—the 5 million registered will have had 2 inoculations?—Mr Walker-Smith I hope that that may be the case, but, as I have already explained, there are many unpredictable factors in this matter and we have to take account of them

Mr M Edelman Does the Minister recall that last year the Pasteur Institute was willing to supply large quantities of Lepine vaccine but that he took no action whatsoever? Does he also recall that the Prime Minister wrote to me last summer saying that there would be discussions between the Ministry of Health and French health authorities in order to make this vaccine available? Will the Minister say finally whether he or his predecessor, either directly or indirectly, ever gave any undertaking to Glaxo or Burroughs Wellcome that he would give them priority over potential overseas suppliers of vaccine?—Mr Walker-Smith I am not aware of any such undertaking in regard to priority He may be thinking of the recommendations of the Medical Research Council that British vaccine should be regarded as our main, permanent source of supply and that Salk vaccine should be regarded as a temporary supply In regard to French and other sources of supply, there would be many technical considerations involved before they could be brought into use—considerations which do not arise in the same sense with Canadian and American sources of supply It seems better, therefore, to get our supplies from transatlantic sources

Mr G R Chetwynd asked the Minister what was the cost of the purchase of anti-poliomyelitis vaccine purchased to date, giving separate figures for imported and other supplies —Mr Walker-Smith replied The total cost of supplies of poliomyelitis vaccine distributed to date in Great Britain is approximately £$1^{3}/_{4}$ million, between a third and a quarter of this amount was paid for imported supplies Mr Chetwynd Can the Minister give an assurance that the availability of this vaccine, both from home supplies and overseas, has not been held up or delayed in any way by a shortage of dollars or lack of resources for development of production at home?—Mr Walker-Smith There is no particular difficulty in regard to money In the estimates for 1958-59 £2 million is included for this purpose and represents 10 million doses If it should be necessary to have more vaccine, I am sure the House will be sympathetic to the submission of a supplementary estimate for that purpose

Mr Chetwynd asked the Minister the nature of the tests used before imported anti-poliomyelitis vaccine is issued to local authorities, and how long they take —Mr Walker-Smith Salk vaccine is tested by the manufacturers for safety, potency, and sterility in the country of origin The United States Government arrange, in addition, for safety tests and for potency tests The potency tests are on monkeys and the safety tests on tissue cultures and on monkeys The tests carried out by the Medical Research Council in this country comprise safety, potency, and sterility tests, involving safety tests on monkeys and on tissue cultures, and potency tests on monkeys The Medical Research Council tests may take up to twelve weeks, but are often completed in ten or less Mr Chetwynd While recognising the absolute need for safety in this matter, is it necessary to have a duplication of these tests and is it necessary for them to take quite so long?—Mr Walker-Smith The question about the necessity for duplication of tests merits consideration in the circumstances It is a fact that the record of the American tests has been increasingly reassuring over recent periods

Protective Clothing and Purchase Tax

In response to almost twenty questions asking why purchase tax was being imposed on miners' protective helmets and footwear and what revenue it would raise, Mr J E S Simon, financial secretary to the Treasury, replied The estimated yield of the proposed 5% tax on these boots and helmets is of the order of £100,000 per annum But the revenue to be raised was not a significant factor My right hon Friend proposed this change as part of a rationalistion of the purchase tax, which also involved reductions of the tax on miners' caps from 10% to 5% and on miners' belts from 30% to 5%

Mr Thomas Williams If the object of this tax was not the revenue to be derived therefrom, what was the other purpose? Does that other purpose justify imposing any duty on protective clothing such as these shoes and caps?—Mr Simon Where there is an anomaly in a tax, it involves unfairness and discrimination between one citizen and another Protective clothing was already taxed Members have had an opportunity on many occasions of discussing whether all protective clothing should be exempt, and it has not been found possible to do this

Mr G O Sylvester Is the Financial Secretary aware that this taxation will cause deep resentment in the coalfields, especially in view of the figure that the tax will yield, which is nothing when compared to the amount of accident to life and limb which these commodities have prevented and which happened in the old days when the men wore ordinary clothing?—Mr Simon I sympathise very much with what the hon Gentleman says, but I hope it will be understood that the tax is part of a larger transaction which includes reductions in purchase tax on some of the articles used by miners

Mr William Stones Is the Financial Secretary aware that many people in the mining industry have spent much time in recent years trying to persuade and encourage men who work underground to discard their prejudices and their cloth caps and to wear safety helmets and boots? Is he further aware that the people to whom I refer are deeply concerned about the possibilities of this imposition of purchase tax being likely to interfere with their efforts to persuade men to wear protective equipment, particularly in view of the meagre amount likely to be saved?—Mr Simon I know of these efforts, and I should be very sorry if they were in any way affected, but I should remind the House that the tax on protective helmets will be under 6*d*

Obituary

FRANK HAMILTON LACEY

T D, M D Manc., F R C O G

Dr F H Lacey, honorary consulting gynæcologist to the Manchester United Hospitals, died at his home in Sussex on April 11

He was born in 1879, the son of Dr T S Lacey, who practised in Oldham and Manchester Frank Lacey studied medicine at the Victoria University, Manchester, qualifying in 1906 He was resident obstetrical surgeon at St Mary's Hospital from 1908 to 1912, and later he served as anæsthetist and registrar His association with St Mary's was interrupted by his service with the R A M C during the 1914–18 war, but on his return to Manchester he was appointed to the honorary staff, and he remained an active member until his retirement in 1946 He was also consultant gynæcologist to Crumpsall Hospital and gynæcologist to the Christie Hospital For many years he was clinical lecturer at the University of Manchester He was a foundation fellow of the Royal College of Obstetricians and Gynæcologists

R N writes of his old chief

Dr Lacey endeared himself to his patients because of his real care and concern for them and his unending patience to ensure their welfare To the hospital staff he was known as Pop Lacey His cheerfulness and kindness made him liked by all who worked with him He took a keen interest in the teaching of both medical students and midwives, and I am sure many remember him as a teacher, for his style was rather novel His lectures and tutorials were rather in the nature of a continuous viva interspaced with graphic illustrations, usually of situations both medical and social which the students might meet in later life He was a raconteur par excellence, and the situations were often highly humorous with solutions a little removed from medicine Outside our profession he had many interests and one of his favourite pastimes was the training and racing of greyhounds

Despite a severe illness shortly before he retired, he recovered a degree of good health which allowed him to fulfil his lifetime's ambition—to be a farmer Leaving Manchester he moved south, and "down on the farm" he enjoyed many years of active retirement as a very good farmer He was devoted to his family, and in his home life was extremely contented and happy You always left his house with a deep impression that it was a real home, and that may have been the secret of his happy and cheerful outlook, for though quick of temper he quickly forgave any mistakes we young residents might make

GEOFFREY WILLIAM RAKE

M B Lond

Dr Rake, research professor of microbiology in medicine in the University of Pennsylvania and scientific director of the international division of the Olin Mathieson Chemical Corporation, died on April 20 at Princeton at the age of 53 He studied medicine at Guy's Hospital, but he had spent almost all his professional career in the United States

He was born at Fordingbridge in Hampshire and went to King's School, Canterbury He qualified from Guy's in 1927, taking the M B Lond with honours the following year After three years working in the department of pathology of Johns Hopkins University under Prof W G MacCallum, he became in 1931 assistant in pathology and bacteriology at the Rockefeller Institute for Medical Research in New York, where he made a special study of meningococcal infection and immunity As a result of this work he was put in charge of the laboratory study of an outbreak of meningitis in a Government camp, and his work in this epidemic led to important results in identifying meningococcus carriers Later he extended his studies to cerebrospinal meningitis and the pathology of pneumonia In 1937 he was appointed head of the microbiology division of the Squibb Institute, and later he became director of the institute and of the Squibb medical division In these new appointments his investigations and interests extended to include the virus and rickettsial diseases and the use of antibiotics He travelled widely in the Far East studying new pharmaceutical preparations and surveying research facilities In 1953 he visited India at the invitation of the Government, and the following year he was a guest lecturer at Taiwan National University He was also director of a research project on anaplasmosis which was jointly sponsored by Mexico, the United States, the University of Pennsylvania, and E R Squibb and Sons de Mexico In 1955 with Dr Harvey Blank he published *Viral and Rickettsial Diseases of the Skin, Eye, and Mucous Membranes of Man* Two years ago he visited London and returned once more to his old medical school

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Diary of the Week

May 4 to 10

Sunday, 4th

University College Hospital, Gower Street, W 1
10 15 A.M Meeting for general practitioners, arranged by the consultant staff of the Royal Ear Hospital, on Common E N T Troubles in General Practice

Monday, 5th

Wright-Fleming Institute of Microbiology, St Mary's Hospital Medical School, W 2
5 P M Dr Deborah Doniach Thyroid Auto-immunity and its Clinical Implications
Hunterian Society
7 30 P M (Talbot Restaurant, London Wall, E C 2) Mr C R. Rudolf Hunteriana Part IV

Tuesday, 6th

Royal College of Surgeons of England, Lincoln's Inn Fields, W C.2
5 P M Prof H Rocke Robertson (Vancouver) Observations on Wound Infection (*Moynihan lecture*)
Postgraduate Medical School, Ducane Road, W 12
4 P M Dr F Avery Jones Ulcerative Colitis
Institute of Dermatology, Lisle Street, W C 2
5 30 P M Dr G B Dowling Scleroderma and Dermatomyositis

Wednesday, 7th

Royal Society of Medicine, 1, Wimpole Street, W 1
5 15 P M *History of Medicine* Sir Arthur MacNalty Alexander Pope, Poet and Cripple Mr W R LeFanu Dr Arbuthnot
8 P M *Surgery* Mr A D Wright Historical Operations (Presidential address)
Postgraduate Medical School
2 P M Dr Martin Bodian Pædiatric-neoplastic Disease
Institute of Diseases of the Chest, Brompton, S W 3
5 P M Dr W D W Brooks Manifestations of Carcinoma of the Bronchus
Institute of Dermatology
5 30 P M Dr R W Riddell Histological Diagnosis of Fungus Infections
Assurance Medical Society
5 P.M (11, Chandos Street, W 1) Dr D D Reid Occupation and Residence in Relation to Expectation of Life
University of Oxford
5 P M (Radcliffe Infirmary) Prof William Doolin Abraham Colles and His Contemporaries (Litchfield lecture)
Manchester Medical Society
4 15 P M (Medical School) *Sir Eric James Education of the Scientist*
Medico-Chirurgical Society of Edinburgh
8 30 P M (18, Nicolson Street.) Prof John Crofton The Altered Outlook on Tuberculosis

Thursday, 8th

Institute of Dermatology
5 30 P M Dr Phyllis Wade Radiation
Liverpool Medical Institution, 114, Mount Pleasant, Liverpool, 3
8 P M Dr E N Chamberlain *The African Slave Trade.*
Honyman Gillespie Lecture
5 P.M (University New Buildings, Teviot Place Edinburgh) Mr Hugh Dudley Neuro-endocrine Response to Injury
University of St Andrews
5 P M (Queen's College, Dundee.) Prof James Walker Physiological Studies in Human Pregnancy

Friday, 9th

Postgraduate Medical School
10 A.M Mr G K McKee Artificial Hip Joints
Institute of Laryngology and Otology, 330, Gray's Inn Road, W C 1
3 30 P M Dr D A Osborn Blood Diseases in Ear, Nose, and Throat Conditions
Royal College of Surgeons of Edinburgh
3 45 P M Mr J G Murray Responses of Nervous Tissue to Injury and Disease, Recent Advances in Knowledge (Sir David Wilkie lecture)

Saturday, 10th

Midland Thoracic Society and North Western Tuberculosis Society
11 A M (Cheshire Joint Sanatorium, Market Drayton) Prof W F Gaisford, Dr H J T Ross Intra-thoracic Primary Tuberculosis in Children
4 P M Dr L Caldwell, Dr G R W N Luntz Pulmonary Tuberculosis and Diabetes Mellitus

Notes and News

IMPERIAL CANCER RESEARCH FUND

At the annual general meeting of the Fund on April 29, the annual report[1] was presented The council has decided to appoint a director, to be in charge of all the Fund's research activities, and Prof G F Marrian has accepted this appointment Permission was received in January to demolish nos 44–46, Lincoln's Inn Fields, to make way for new laboratories and offices, for which detailed plans are being prepared

Among much research reported is a clinicopathological study of prostatic cancer Three groups of patients are being compared those who die within three years, whatever the treatment, those treated with hormones and surviving five years or more, and those who survive over five years untreated It is thought that in the first group the effects of treatment may be non-specific, and due to relief of obstruction or of sepsis, while the survival in the other groups may be due to retardation of growth—by treatment in the second group and by some natural mechanism in the third group These ideas are being tested by clinicopathological observation of patients, including measurement of hormone excretion in the urine before and after treatment In more than two-thirds of a group of cases of cancer of breast and prostate, an association is thought to have been found between the clinical course during additive or ablative hormone therapy and the fluctuation in the amount of œstrogen excreted in the urine The absence of an association may be due to hormone-independence or to stimulation of tumour growth by hormones other than œstrogen[2] In many cases removal of the gonads, adrenals, and even pituitary did not completely eliminate hormone production, the biological significance of the small amounts remaining is not known

SOUTHPORT'S NEW MENTAL HOSPITAL

On April 15, Dr G E Godber, deputy chief medical officer of the Ministry of Health, inaugurated the first phase of Greaves Hall Mental Deficiency Hospital at Banks, near Southport The new hospital was, he said, a sign of our awakened sense of responsibility for the welfare of the mentally afflicted Its purpose was not to take people in and keep them for the rest of their lives but to restore as many as possible to life in the community

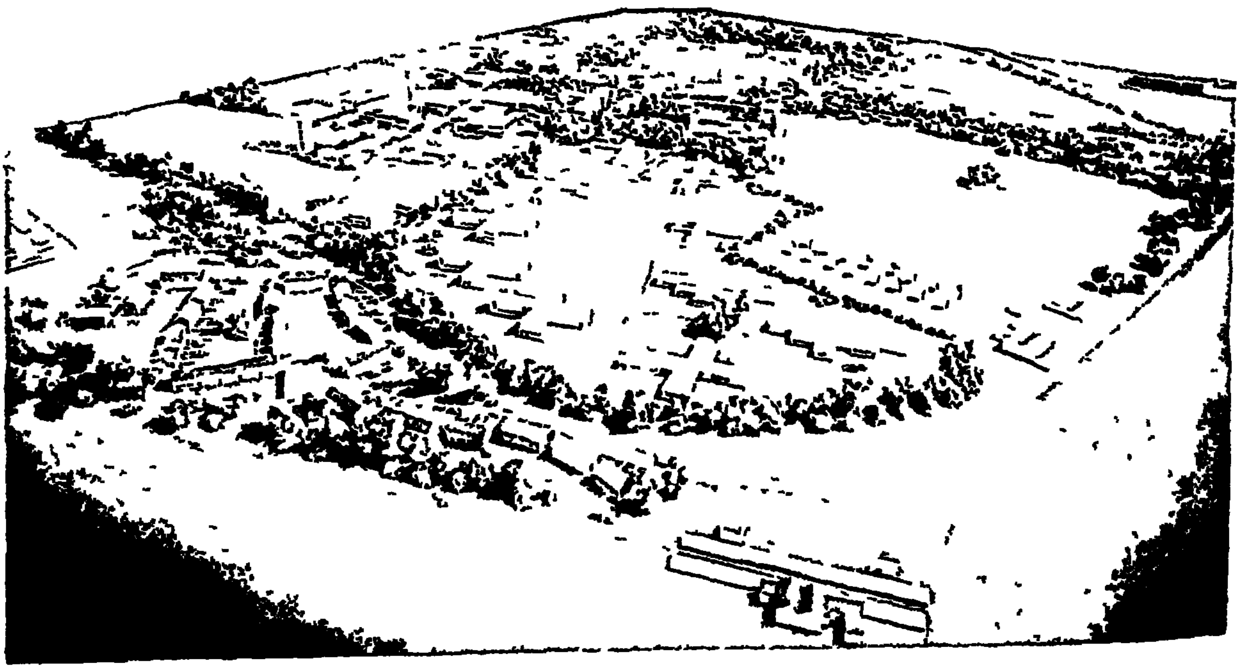
The new hospital, which is to cost £3 million and to house 1000 patients, stands on the main Preston-Southport road within easy access of Southport itself and of the industrial area of Merseyside Since 1939 Greaves Hall, from which the new hospital takes its name, has been used as a mental hospital, and at present it houses 170 patients The hall itself will later serve as the administrative offices of the new hospital The patients will be distributed among 20 villas which will be scattered over the 150-acre estate 4 villas have already been built and 2 are nearly full It is also intended to build 70 staff houses The tree-lined avenues, spinneys, coverts, and ornamental gardens of the estate are being preserved wherever possible

Work on the first phase of the development began in 1955, and besides the 4 villas for patients mentioned above has included a boiler-house, water tower, control point, nurses' home and 28 staff houses Work on the second phase is expected to begin in the autumn and will include another 8 villas, central kitchens, dining-rooms, laundry, workshops, garages, a school, recreation hall, gymnasium, and farm buildings The third and final phase will provide more villas for patients and a general hospital for the institution

MEMORIAL TO KATHLEEN FERRIER

At a ceremony at University College Hospital on April 24 Sir Henry Dale opened the Kathleen Ferrier extension of the radiotherapy department and unveiled a plaque of the famous singer by Mrs Mary Gillick The Kathleen Ferrier Memorial Fund had made possible the extension to this part of the hospital where she was treated, and in addition to contributing to the cost of building and equipment, the Fund also provided for certain technical staff The equipment in the new extension includes apparatus for studying the effect of oxygen in enhancing the action of radiotherapy for malignant disease

Sir Henry Dale and Sir Benjamin Ormerod both spoke of the warmth and vitality that had made Kathleen Ferrier so memorable a person, even apart from the beauty of her voice Sir Benjamin recalled particularly vividly two of her concerts, one at the Royal Festival Hall when she sang in *Das Lied von der Erde*, and another in Manchester when Sir John Barbirolli and Dr Bruno Walter shared the conducting of *Messiah* Mr Myles Formby referred to the distinguished work that had



Model of the institution when completed

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[1] Imperial Cancer Research Fund Fifty-fifth Annual Report, 1956-57 Issued by the Fund, Royal College of Surgeons, Lincoln's Inn Fields, London, W C 2

[2] Hadfield, G *Lancet*, 1957, i, 1058

been done in the radiotherapy department under the direction of Dr Gwen Hilton and which could now be expanded thanks to the efforts of those who had initiated and supported the Memorial Fund Among those present at the ceremony were Dame Myra Hess and Mr Hamish Hamilton

PHYSICIANS IN CONFERENCE

THE Conference on Anæmia and the Alimentary Tract, to be held by the Royal College of Physicians of London on July 25 and 26, is an interesting departure In devising this meeting, which, if it proves successful, may be the first of a series, the college has aimed not so much to engage in postgraduate training as to provide a means for the information of consultants, who will be able to exchange views informally, and the details of this first meeting, announced in our advertisement columns this week, make it clear that most of the speakers are themselves furthering knowledge of the subject.

A NEW CAUTIONARY CARD

WE have referred [1] to cards that are, or might be, carried by people with chronic illnesses to warn doctors about their condition in case of emergency, and we suggested that such cards might be used by those taking long courses of such drugs as cortisone, ganglion-blocking agents, and antibiotics The American Heart Association (44, East 23rd Street, New York 10) has produced a card, designed as a wallet insert, for people having long-term anticoagulant treatment. It specifies the drug that the bearer is having, and his blood-group, and gives advice on what to do in emergency illness or accidents

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University of Oxford

It is proposed to confer the honorary degree of D SC on Dr Arne Tiselius, professor of biochemistry in the University of Uppsala

University of Edinburgh

Dr Alan Peters has been appointed lecturer in anatomy

University of Glasgow

On April 26 the degree of M.D was conferred on the following

William McNaught, A J O Hea and A A Robin (*with commendation*), Bernard Camber, Ella I McNaught

Dr M. G P Stoker, Huddersfield lecturer in special pathology in the University of Cambridge, has been appointed to the new chair of virology at Glasgow

Dr Stoker, who is 39 years of age, studied medicine at Cambridge and St Thomas's Hospital, qualifying in 1942 After holding a house-appointment at Lambeth Hospital he served with the R.A M C and took part in typhus research in India In 1947 he became assistant pathologist at Addenbrooke s Hospital, Cambridge He was appointed to his present lectureship in 1948 He is also director of medical studies and assistant tutor at Clare College He is a member of the World Health Organisation s expert advisory panel on zoonoses, and his published work includes papers on Q fever and other rickettsial and virus diseases

National University of Ireland

The following appointments have been made at University College, Dublin

Dr T B Counihan, professor of medicine, Dr D K. O Donovan, professor of medicine, Mr Eoin O'Malley, professor of surgery, Mr P A. FitzGerald, professor of surgery, Dr J W Harman, professor of pathology, Dr P J Cannon, professor of pharmacology, Dr Oliver FitzGerald, professor of therapeutics, Dr P N Meenan, professor of microbiology as applied to medicine

Louis Rapkine Lecture

This lecture will be given by Dr Jacques Monod of the Institut Pasteur, Paris, on Monday, June 2, at 5 15 P M, at the Institut Français du Royaume-Uni, Queensberry Place, London, S W 7 His subject will be the permeases—specific factors of cellular permeability

Royal College of Physicians of London

At a comitia on April 24, with Dr Robert Platt, the president, in the chair, the following were elected to the fellowship

PANDIPEDDI KUTUMBIAH, India, J O MERCER, New Zealand W F CONNELL, Canada J H WALTERS, London S S MISRA India F S BRIEN, Canada SAUL ADLER Jerusalem, THOMAS SIMPSON London WILLIAM GOLDIE Leeds W A OLIVER, Norwich E JOAN STOKES, London J E. CLARKE, Australia, M A RUGG-GUNN London C J C G HODSON London, J L PINNIGER, London, URSULA JAMES, London D DE LA C MACCARTHY, Aylesbury, Bucks J P M TIZARD, London MARTIN ROTH, Newcastle upon Tyne A T JONES, Liverpool, W S PEART London, H E DE WARDENER, London DAVID STAFFORD-CLARK, London A D CHARTERS, Kenya, P H DAVISON Birmingham S C GOLD London M D MILNE, London, E B ADAMS, South Africa I C K MACKENZIE London S W STANBURY, Hale Barns, Cheshire S T ANNING, Leeds, D H COLLINS, Sheffield, J S I SKOTTOWE Oxford C H GRAY London THOMAS MCKEOWN, Birmingham J S MITCHELL, Cambridge, SIR LINDOR BROWN, London, EDWARD FORD, Australia, SIR HANS KREBS, Oxford

The following having satisfied the censors' Board were elected to the membership.

B I Chazan M.B Glasg , Gordon Cohen M B Cantab , G L Donnelly, M.B Sydney, G H Fairley, B M Oxon., Nellie P Fernando, M B Ceylon, P N Francis, M.B. Sydney, Morris Greenberg M.B Lond C B Hatfield, M.D Alberta, T D R Hockaday, B.M Oxon , R D Hyde M B Cantab , J H Jones, M.B Cantab , G S McL Kellaway M B N Z , R S Kocen M.B Leeds, Albert Kusklick M B W'srand, P J Lachmann M B Cantab , Hermann Lehmann, M B Basle Emanuel Lewis M B. Lond Clifford Mawdsley, M B Manc., R J Mulhearn, M.B. Sydney M J Pritchard, M B Cantab , S B Rosalki M B Lond R W Ross Russell M D Cantab , K F R Schiller, B.M Oxon , Samuel Shuster, M B Lond , George Simon M.D Cantab , I D H Todd, M.B Aberd

Licences to practise were conferred on the following 145 candidates who have passed the final examination of the Conjoint Board

T R Abbott, H B Bailey, Richard Barker J D Barrett, J M Beeley, J T Bench Colin Berry, N D E G Best Biswarup Bhattacharya, Margaret A Birchall J M Black, Sarah M E Blatch, Natalie Bogdan, Mary-Ann M Bolt, M C Bott Patricia M. Bradford R W Bramwell, J F Branton, John Brice-Smith T R. Bull, Shirley F C Burrell Christine M Butler, A J G Campbell, P A Carter, Robert Chapple S E Cheah J H. Chilman, Daphne C K Clarke. Marion Coates R D Cohen D M A Cowie, Sheila M Crawshaw, R H I Crockatt, Patricia E. Crome, P G Darby, A H Davies Ann V Davis, D D Devine, E F Doleman H S Donnelly, E E Douek Jean G Doughty, D C Dukes J G Edwards, L. A Emanuel E. R. Emmanuel, Geoffrey Evans, Patricia Farren F J Fawcett, A V Fox, Ruth Frank Isidore Freedman P M Fullman Ramon Gaertner, J R. Geddes, D W R. George, G R Gerson D H Gill, M. J Goggin, Bernard Goodhead, Dorothy R Gordon, A J Gregory, Janet M Guenault, K C Hammond, J T Harries J S G Hayes, G D Hayter Elizabeth M Hedges Gillian C. Henly J R Heron, A B Hewitt, N F Hill L J Hipkin Michael Hopwood Judith Hornung, G R Horton, Margaret E Hughes, D J Hunt, G B Hunt D A Hutchinson Sheila M V Jeffery R D T Jenkin, G I John G W Jones J F Kane, W E Kearns Delia M Kenyon, J O Kilby, K G Korsah, Obeadum Kusi-Mensah Hilary R G Lennox A J Lupin D R McCoy Antony Magrath, R. T F Maguire G M Makhlouf John Martin, D R Matthes, June Mills, A B Morphy, Evelyn J Moss, Frances A Musson C R Neequaye, David Negus, A D Noble C F W Palmer A J Pechal Norman Peters, Elizabeth J Porter, Arnold Powell P R Preston, J D Price, B J Prout, D J Puddifant, C D P Rhodes, Margaret Richardson, H P Rikard-Bell, C J Roberts E J R Rossiter Naomi J Sage, M D Sidell J B Sorapure, B R. Sparke, C G Stephenson Pamela M Stracey R. C Swan M H Sykes, M A. E. Symonds, D J E Taylor B M Thomas J L E W Thomas, Winifred Tooby J C. Uzoma, C W Venables, M T Ward, Judith C R. Wardle Dorothy West A J Whitley Barbara J Willmer, D N Wood W D R. Writer, J D Wyatt, Shing Yiu Yip, D A. Young J E Godrich

The following diploma and those mentioned in our issue of April 26 (p 918) were conferred jointly with the Royal College of Surgeons

D C.H—G P Anthony C P Anyon, Mary C Armstrong Saraswati Arora, Kanchana Arunlakshana C S Ayoub P A Barker, Norman Beenstock, Edith Bergel Marjorie L. Bowen K D Boyd, Marjory H Boyle Margaret E Broughton Alison G H Brown, T F Bushby, Josephine H Calder Enid G Carson H J W Cleeve Iain Crawford, Martha E. N Davies, Hymie Davis, W S de Silva, Patricia A Dinkel Patricia J Dockery Sheila M Foster Lise L Fowle Gillian M Gandy M B Gee, S S Ghatak, D C Gill Catherine E. Hall, S M Haneef, B R. Hardwick-Smith, Audrey M Hillary, Badruddin Ibrahim, Constantinos Ioannou M L M Izzadeen, R B Jahina C R Jayachandra, Emily M Kerr Hilda Koilpillai Kathleen M Laing Kathleen M Lamont, Alice Latham, H A McClelland Kathleen L. MacGregor, Irene E McLaren, Dorothy Mainwaring J R MacG Millar J N S Mitchell Wendy L Mitchener, Y P Narula E I F Nashawati, P O Nicholas N J O Doherty, M J Page, Dolly I Pakshong Kiramathypathy Paramathypathy, F B W Parker M D Parker, M W Partington Veronica Pearson J D W Peck, Valerie J Perkins T G J Phillips, Philippe T Piens, Mavis M Polkinghorne, Srimavadesi Ponnudurai, Dorothy H E Ramsay, S K Ray Pamela A M Rendell Raire E I Roberts Jill P Rosser, S K Roy, Sophie Sash Promod C Sharma Maxwell Shavitsky W H Shaw, P F Sheppard M H Lees S L. Shrikhande J A B Spalding J N Standring Harry Stark Averil M Stedeford R McK Sutherland K H Tan Frances C Thomson Elizabeth M Tilsen M W Tisdall Anne E Treharne Y K Tseung Pia M Unger, S K Vohra, Barbara Ward Jean M Watkins M A. Wenig Catherine M White R. G M Whittaker, R M Whittington, Amarapala Wijenaike Frank Wilson Maudie E Wilson S -E A Wyner, Pamela M Zinkin.

On Tuesday and Thursday, May 13 and 15, at 5 P.M at the college, London, S W 1, Dr Paul Wood will give the Croonian lectures His subject will be the Eisenmenger syndrome, or pulmonary hypertension with reversed central shunt

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1 *Lancet*, 1956, ii 1143

Royal College of Obstetricians and Gynæcologists

The following have been awarded the D OBST

Elizabeth K Adam, Jean M Adams, Isobel A C Alexander, N K Allahbadia, Hilary Allin, I M Allison, Helen M Amsbury, J T Andrews, Christos Angeli, Maureen C Archer, Lyn Ashworth, David Barry, M K Basu Mallik, D H Bayton, P J Bekenn, J D L Bell, Caroline M Benazon, Brenda L Bodenham, Anne Bowles, N M Brown, K W Browne, V R Bruce, G O D Busby, Catherine G Butcher, Anne L Campbell, W J Carter, Georgina M Chadwin, S K Chaudhuri, Jay-Gopal Chitnis, Jean E Clark, B S Clarke, Evelyn Coates, John Colville, Robert Condie, Joseph Connolly, P L Cook, F B Cookson, M N Cox, John Crook, D R Das, I A Davies, J J De Jode, B G Dudley, Ma Tin E, M O'N East, S K El Deiry, D H Elliott, C D'A Ellis, P M Elwin, I M Evans, Mary D Evans, Elizabeth M Everard, Geoffrey Fearnley, Michael Galton, E F D Gawne, Marie P Gilbert, Margaret G Gillan, Mary R. Glyn John, H E Godfrey, A W Gostling, J H Graham-Marr, J D Granger, B H Grant, Lionel Grant, A J Gray, C P Gray, A H Gretton, N D Gripper, Mary E Habgood, R A Harlow, Shaukat Haroon, D M Harris, D T Harrison, B H P Heber, Jon Henderson, J R Hobbs, C J Hopkins, T W Hoskins, W D Jeans, Elizabeth M Jewell, G K Jivani, E R Johns, E T Johns, R H Johnson, G W Johnston, J D Jones, J R Jones, W R B Jones, Niva Joshi, S K Kataria, D H Kay, T J King, R N Kolah, Pamela F Kordik, M R Landeg, J S Lawson, R C Lawson, A F Lee, J D Le Souef, Jean Y MacDougall, J C H McDonald, Janie M McIntyre, J W McLellan, Anne M Macgillivray, Joseph Main, G S Mandal, Charles L Mansfield, G N Marsh, I B Martin, A T Mathew, R H Mathews, Paul Maton Terry, A G May, A MacG Michael, Dennis Milner, R R W Mirrey, Shyamal Mitra, S C Moles, H S C Moore, J A Morgan, Myfanwy C R Morris, C I Moss, S D Mulye, J K Murphy, Mary A B Murray, F J Nash, J E Newcombe, E H Noble, Ma Khin Nu, Liam J O'Brien, A H Padsha, Joyce M Pallett, I W Palmer, M S K Palmer, J C Parkes, P N Paterson-Brown, A J Pearce, T N Pearson, W F Perera, Valerie J Perkins, I S T Phillpotts, G E Pickup, G G Pollock, D R Pratt, O H Proctor, Sheila G Quain, John Quantrill, J C Ramsay, D A Richardson, E H Ritchie, Elizabeth R J Ritchie, G C Rivett, O W Samuel, C R Salisbury, B E Sayers, Bryan Scaife, P H Scott, S K Seal, Monica Shackleton, D Y Sharples, C D G L Shimmin, Vasanti Sikand, A W Simpson, Catherine I Soutter, M G Spark, J M Spence, W L P Spicer, Averil M Stedeford, S J Steele, M D B Stephens, Geoffrey Stout, D S Strachan, M K Strelling, C E Strode, Margaret J D Sturges, B B Taylor, Murugasoo Thillainayagam, A A L Thomas, Vincent Tonge, K H Trigg, Wanda Trowsdale, Jean M Turpin, M S Tyrell, C E Upton, P C Vivian, Marguerita A M Von Bergen, G B Walker, Audrey P Ward, Howard Watson, Patricia J Whelan, M T White, D A Whiting, William Whittingham, B R Wilkinson, C W L Williams, D T A Williams, D G Williams, M G Williams, M J Williams, R D Williams, D J Willsher, A S Wilson, J H Winder, B J Wright, J A Wright, J D Wrighton, Joyce O Yates, R C Young

Queen's Institute of District Nursing

This institute will hold a conference at Church House, Westminster, S W 1, on Tuesday, May 6, at 2 30 P M , when Dr J A Gillet and Dr John Fenton will speak on ageing and the over-60's and schemes for the employment of elderly people

Institute of Child Health, London

On Tuesday, May 27, Dr G M Guest, of the Children's Hospital Research Foundation, Cincinnati, will give a lecture on studies of insensible weight loss, and on Tuesday, June 24, at 5 P M Prof J H P Jonxis, professor of pædiatrics at the State University, Groningen, will speak on diseases due to abnormal hæmoglobins The Simpson Smith lecture will be given on Wednesday, July 23, by Dr W J Potts, surgeon in chief of the Children's Memorial Hospital, Chicago His subject will be congenital atresia of the œsophagus All the lectures will be given at 5 P M at the Institute, The Hospital for Sick Children, Great Ormond Street, W C 1 Tickets for the Simpson Smith lecture may be had from the dean of the institute

Wellcome Trust

Among the grants totalling £108,630 sanctioned by the Wellcome Trustees for the half-year ended March 31, 1958, were the following

Institute of Cancer Research, University of London—£40,000 for the cost of including a Wellcome Laboratory of Pharmacology and Experimental Chemotherapy in the proposed extension of the Chester Beatty Research Institute

Government of Kenya—Up to £10,000 for the cost of adding a Wellcome Research Library to the Medical Research Laboratories at Nairobi

Nuffield Department of Surgery, University of Oxford—About £16,500 for the purchase of a Gibbon-Mayo heart-pump for use in research on the surgery of the heart

Department of Pharmacology, University of Sydney, New South Wales—About £3000 for a scintillation spectrometer for work with radioisotopes

Department of Pharmacology and Therapeutics, University of Manitoba, Winnipeg—£13,000 to provide the stipend of a Wellcome research fellow for six years

International Congress of Balneology

This congress will be held in Marienbad, Czechoslovakia, from Sept 8 to 13 Further particulars may be had from the secretary of the congress, Reznicka 5, Prague 2, Czechoslovakia

Institute of Hospital Administrators

The Institute is holding its annual conference in London, in conjunction with the International Hospital Equipment and Medical Services Exhibition, from May 5 to 7 at the Empire Hall, Olympia Further particulars may be had from the secretary of the Institute, 75, Portland Place, W 1

Electrophoresis in Clinical Biochemistry

The southern region of the Association of Clinical Biochemists and the Society for Analytical Chemistry will hold a joint meeting on this subject on Wednesday, May 7, at 7 P M at Burlington House, Piccadilly, London, W 1 The speakers will be Prof N H Martin, Dr W G Dangerfield, and Dr A L Latner

Rockefeller Foundation Grants

During the first quarter of 1958 the Foundation distributed $4,300,000 Grants for medical education and public health amounted to $910,000, and for biological and medical research $576,000 The grants include $33,500 to the Welsh Regional Hospital Board (over five years) to continue aid for research on the biochemistry of the nervous system under Dr Derek Richter at the Neuro-psychiatric Research Centre at Whitchurch Hospital

British Association of Physical Medicine

At the Association's annual dinner, held in London on April 25, Prof Robert Platt, F R C P , remarked that one of its objects was the achievement and maintenance of physical fitness He owned that his own idea of physical sport was a good hard game of chess health must not be confused with strength Continuing more seriously, he said that, with the growth of knowledge and techniques, specialisation was inevitable, but specialisation should not interfere with the relation of patient to doctor, *which belonged to the art of medicine* and not to any particular specialty Today medicine was more satisfying than ever before, because so much of science was at its command There used to be much humbug Now there was no need for pretence the profession could be frank about what it knew and what it did not know Professor Platt observed that if he had to found a new society (which, he added, heaven forbid) he would name it SAGIM—the Society for the Abolition of Gloom in Medicine The National Health Service had its faults, but it should not be blamed for everything Dr Philippe Bauwens, the president, responding to Professor Platt's toast of The Association, reported that this had had a good year Dr Hugh Burt spoke well of The Guests, and Dr Ian Grant, president of the College of General Practitioners, responded

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Sir Oliver Franks has been appointed chairman of the board of governors of the United Oxford Hospitals

Prof Richard Ellis and *Dr Bernard Schlesinger* are visiting Turkey, under the auspices of the British Council, to attend the National Seminar on Child Health Problems

A meeting of the West Midlands Physicians Association will be held at Burton-on-Trent General Hospital on Saturday, May 31, at 11 A.M

The Society for Music Therapy and Remedial Music, which has been set up to promote the use of music in the treatment, training, and reablement of children and adults with emotional, physical, or mental handicaps, is holding its first meeting this Saturday, May 3, at 3 P M at Overseas House, Park Place, St James' Street, London, S W 1 Prof W A Robson is the chairman and the hon secretary is Miss Juliette Alvin (6, Westbourne Park Road, W 2)

A booklet, containing abstracts of papers submitted for the Benger prizes for original observations in general practice, has been published by Benger Laboratories, Ltd Copies (5*s*) may be had from the College of General Practitioners, 54, Sloane Street, London, S W 1, proceeds from the sale of the book will be passed to the college

The Lancet · Saturday 10 May 1958

MEASUREMENT IN MEDICINE

MAX HAMILTON
M D Lond , D P M
SENIOR RESEARCH FELLOW, DEPARTMENT OF PSYCHIATRY,
UNIVERSITY OF LEEDS

LITTLE more than a century after the birth of scientific medicine the present day is seeing the beginnings of a new revolution—the infiltration of the ideas and methods of modern experimental biology In all branches of medicine a drastic fundamental re-examination of even the longest-held cherished ideas and practices is pursuing its iconoclastic way, and many of these practices, when weighed in the balance, are found wanting

These new ideas and methods are to be seen most clearly in the field of research, where they take the form of an increasing insistence on the proper design of experiments and statistical analysis of results The clinical trials initiated by the Medical Research Council have given a lead in this field and set appropriately high standards The same trends are visible also in clinical medicine, where they have appeared most prominently as an increasing dissatisfaction with the basis of clinical judgment, the rediscovery of " observer error ", and a rather unsophisticated demand for the replacement of clinical observation and judgment by mechanical or " instrumental " methods Particular emphasis has been placed on " observer error " in the assessment of radiographs of the chest, but, of course, the problem is a general one A consideration of the fundamentals of this general problem should help in solving current difficulties

I intend to show here, by starting with an analysis of the fundamentals of measurement and error, that clinical judgment and observation do not merely form an inaccurate method of doing something which ought to be done better, but have a legitimate and irreplaceable function in medicine

Nature of Measurement

Measuring things is such a familiar activity that its nature appears to be self-evident Only philosophers worry about it

The simplest form of measurement is that in which a population is divided into two classes with and without a given attribute, each individual is, in effect, compared against a standard which has or has not the attribute In a sense each individual acts as a standard For example, we may classify persons in the street into those who are and those who are not wearing a raincoat The common numerical equivalent of such qualitative dichotomies is that of 0 and 1 The average for the group represents the probability of finding an individual with the attribute

A slightly less simple form of measurement is that in which the two classes differ on the basis of intensity of attribute All members of the population possess it, some more and some less For example, we may divide the population of men into those eligible and those not eligible for admission into the Police Force, in so far as they do, or do not, exceed a given height This division could be made by comparing each individual with a standard individual who is of the lowest eligible height In practice a ruler is used, being equivalent to the standard individual as regards the particular quality under consideration

Instead of two classes the population may be divided into three or more classes, and in that case several standards will be required The easiest way of supplying these standards is to use the members of the population as standards Each individual is then compared with the others and judged to be greater or less In this way the individuals can be ranked in a series in which the number of classes equals the number of individuals The number of classes can be reduced by bringing together adjacent individuals into one class, and can be finally reduced to the lowest subdivision of two classes This case reduces to the simpler procedure already described

The arrangement of members of a population in an order is not restricted to one quality A complex of qualities can be equally dealt with, as when it is decided that one patient is more ill or more in need of emergency treatment than another Individuals can be placed in order of rank as regards more than one quality, but then the order will not necessarily be the same If several qualities give rise to the same rank order, these qualities are probably not truly distinct and may perhaps represent different manifestations of the same essential or underlying quality This point, and the problem introduced by errors which interfere with the " true " ranking, will be considered below

The methods described so far enable us to make comparisons only within the population dealt with If we wish to compare one population with another, we must have some method of reproducing the standard This is not necessary where the individual members of one population can be compared with those of the other, but this is equivalent to saying that all the individuals can be assembled into one population The essential point emphasised here is that measurement in its simplest form does not necessarily imply a standard which is reproducible in different places and different times Such a reproducible standard is required only when comparison is between one population and another

The usual method of making the comparison which is the basis of measurement is to observe together the standard and the individual to be measured The comparison is " side by side " This is not always possible, and in medicine it is common for the standard to be not only absent but also impossible to obtain Thus, when we compare a patient's present state with what he was previously, it is impossible to make a direct comparison Comparison here is between the individual as observed and as he is remembered either by himself or by the physician This method of comparison against a remembered standard is extremely common, both inside and outside medicine For example, the possessor of " absolute pitch " can compare any note he hears with the notes of the scale which he remembers, and can identify its position exactly Length can be similarly measured One can judge a person's height with reasonable accuracy and in seaside resorts and fairs one can find people who earn a living by judging a person's weight in the same way

There are other reasons why a comparison by simultaneous observation is not made, the commonest one is that in which simultaneous observation is impracticable—e g , when two musicians are compared on the playing of the same piece of music Another reason is that the standard is so complex that it is impracticable to make it For example, the radiologist judges a radiograph of the chest to be normal or abnormal, and he does so by comparing it against a "standard radiograph" of a normal chest Since no two chests are alike, the standard is more or less a sort of "average" obtained over the course of years and present only in the radiologist's mind It must not be forgotten that a chest can be abnormal in many different ways The physician listening to heart sounds or palpating an abdomen is in a similar position to that of the radiologist

It is often assumed that measurement requires a second characteristic the individual measures should be additive The classical example of such additive measures are those of length and weight Thus 5 cm and 1 cm not only equal 6 cm but also equal 4 cm plus 2 cm, and 3 cm plus 3 cm The same applies to pounds and kilogrammes This additiveness is never completely true in all circumstances, and in most cases is rarely so Even in the obvious example, that of distance, it is untrue when the distances become large enough Thus a traveller who goes 10,000 miles away from his home and then a further 10,000 miles in the same direction is not 20,000 miles from home but 5000 miles from it If he goes another 5000 miles he will be at his home It might be said that this is so only because the earth is spherical, but, according to the theory of relativity, the same is true of the Universe as a whole, and the Universe, by definition, has nothing else outside it In fact, many of the measures in science are not additive Thus two specific gravities cannot be added together

Theory of Errors

It may be laid down as a general principle that all observations (and these include measurement) are subject to error For the present purpose errors may be subdivided into two groups those due to errors of measurement, and those due to sampling of population Errors of measurement may be subdivided into random errors and bias There are special problems associated with the type of measurement that consists of comparison against a remembered standard

Bias

Bias is produced by several factors, some of which are well known and can be dealt with, and others are less understood One of the most important is that the standard may shift for various reasons For example, if the observer examines a series of objects which change regularly in one direction (perhaps from normal to abnormal) by very small amounts, adaptation, which may be sensory (peripheral) or psychological (central), may shift his standard An important example of this is the anæsthetist's difficulty in observing the appearance of cyanosis when it develops slowly The reverse movement of the standard may be produced when extreme examples appear Thus, minor signs may be regarded as positive, until the observer sees several examples of major signs, after which he will tend to disregard minor ones The classical example of this is the examination for finger-clubbing in the chest clinic

All such processes are psychologically an assessment of differences, and the minimum of perceptible difference is determined by several factors One of them is the direction of approach, and, where it is necessary to eliminate this bias, it is usual for measurements to be made by approaching from both directions For example, the astronomer measuring the position of a star on a photographic plate makes repeated measurements in half of which he moves his microscope to the star from the left and in half from the right Such methods of increasing the accuracy of his measurements are particularly important because the image of a star produced by a telescope consists of a small disc surrounded by concentric circles The centre of the small disc cannot be accurately found because its edges are not clear, and the random distribution of silver grains in the emulsion makes its outline difficult to define

Attempts to eliminate bias in clinical medicine are not always made Thus the old method of estimating blood hæmoglobin of necessity introduced the bias of direction The concentration of hæmoglobin was determined by putting a fixed quantity of blood, saturated with carbon monoxide, into a standard tube and diluting it gradually until it matched the standard specimen The result obtained by diluting a concentrated solution will always tend to be different from that obtained by going in the reverse direction—i e, by adding successive minute quantities of blood to a fixed quantity of water until its colour matches the standard

Bias may even be useful sometimes The minimal perceptible difference will be increased by fatigue but diminished by expectation, hence an observer who is expecting a change will detect it sooner than one who is not When a clinician takes a patient's history, it may predispose him to take notice of slight signs which might otherwise be ignored It is partly for this reason that the clinician emphasises the importance of taking a good history first and using it as a guide to further investigations, as opposed to starting off with a series of routine tests

The traditional procedure for percussing the heart illustrates this very well In the first place the history indicates whether the heart is likely to be affected and its size or position altered The physician then palpates the chest to detect the apex-beat, and this sets one limit to the outline of the heart He then percusses the upper level of the liver, partly because it is usually in a fixed position and partly because the contrast between lung and liver is the maximum that can be obtained in the chest The physician has therefore, as it were, anchored his observations within certain limits and defined standards for the observation of small differences The results of percussion are usually reasonably good

Enthusiastic sceptics have made occasional attempts to determine the accuracy of percussion by asking clinicians to percuss one side of the heart without any of the usual preliminaries The results usually demonstrate that such percussion is practically useless One can sympathise with those clinicians who so good-naturedly allowed themselves to be placed in an unfavourable light, but one must still consider such so-called investigations as irrelevant

There is a story of one such "inquiry" in which the physicians were asked to outline the heart of a cadaver from which the heart had been removed from behind The story goes that they did not notice what had happened If the experiment were to have any value at all, it should have been done on one of two cadavers, and the physicians asked to compare the two and to account for the differences, if any This would have demonstrated what every clinician already knows, that percussion is appropriately informative in the right circumstances

Bias cannot be eliminated by subjective attempts to correct it, because this may produce bias in the reverse direction or, as it is usually called, "leaning over backwards" It can be reduced by methods of measurement which diminish the range for the play of subjective judgment, but they cannot eliminate it For example, mobility and range of movement in a joint can be estimated by an observer, but the use of a protractor will tend to make the measurement more accurate Even then movements of the joint can be increased or diminished by enthusiasm or lack of it on the part of the patient and his physician, because often the limitation to movement is due to pain, which is extremely sensitive to emotional state For this reason it is now well recognised that, in clinical trials, the treatment should be given as a "double blind"—i e, neither the patient nor the physician knows which of two different treatments the patient has been given The method fails when the treatments give such very different results that they can be detected easily, but in that case such precautions are unnecessary On the other hand, serious difficulties arise when the results of the two treatments do not differ greatly, but they can be identified by the different side-effects To deal with this requires not an understanding of statistics or experimental design but an intimate acquaintance with the clinical phenomena under investigation and the problems of dealing with them

The shifting of the standard in the course of a series of observations can be corrected by designing an artificial reproducible standard and by comparing each observation with it This is the method used by H G Wolff and his collaborators for measuring the degree of injection of gastric and colonic mucosa

If anæsthetists thought it necessary to notice the appearance of cyanosis at the earliest possible moment they could do so by devising a gadget consisting of a red background, the colour of oxyhæmoglobin, which could be covered by one or more layers of opalescent material to simulate the skin, and by a buff transparent sheet to imitation pigmentation In this way the anæsthetist could make a match for the appearance of the patient's ear and cheek before operation, and use it during the operation to detect the first appearance of cyanosis

Temporary shifts of the standard due to the nature of the material examined can be reduced by dealing with small batches at a time and starting off by two standard specimens—e g, radiographs, one of approved normal and the other abnormal Failing such standards, it is a great help to make careful accurate detailed definitions of normal and abnormal, and to read them through before starting each batch

Random Errors

Since bias is, by definition, those sources of error which tend to alter measurement in one particular direction, all other sources of error are random errors, and the theory of errors is concerned largely with them In its simplest form it deals with the large number of possible causes which will tend to disturb a given measurement by a small amount (Large disturbances must be eliminated in the experimental design) These small sources of disturbance are independent (because if they are not they become one source in effect) and tend to increase or to decrease a given measurement according to the direction whence they come or, alternatively, whether they are absent or present If they all act together in one direction, there will be a large error, if they act together in the opposite direction, a large opposite error will appear, and, if they act in opposite directions, the effects will tend to cancel each other out On these assumptions it can be shown that large errors will occur rarely and small errors frequently, and the distribution of these errors will be that commonly called gaussian or "normal"

If a graph be plotted of the frequency with which the different measurements occur it will be bell-shaped Since the errors tend to be in either direction, in the long run they will occur equally in both For this reason the simplest method of eliminating random error is to take many observations and to use their average (mean) as the "true" measurement An illustration will make this clear and show the underlying complexities in practice

A single measurement of a patient's blood-pressure is so liable to error that it is of little value in practice If it is important to obtain as accurate an estimate as possible, the measurement should be repeated several times and the mean calculated How often should the measurement be taken ? This can only be answered in a statistical sense, the greater the number of measurements from which the mean is derived, the more reliable is the mean, and its reliability can be described in a statistical sense This in itself may not be sufficient, for the observer himself may be liable to bias and random error The latter is part of the total random error and need not be further considered, but the observer's bias can be eliminated only by comparing his measurements with those of other observers If all observers were equally biased in one direction, the term true measurement—i e, measurement without observers' bias—ceases to have meaning, but, if they differ either in amount or direction or both, bias can be eliminated by using many observers and taking the mean of the observers Thus the best estimate of the patient's blood-pressure is the mean of measurements made repeatedly—e g, daily—by many observers, and its accuracy can be determined by the usual statistical methods

The customary way of recording such results is to place all the measurements made by one observer in a row, the measurements by another observer in a second row, and so on Thus each row represents the measurements made by one observer, and each column represents the measurements for a given day The mean of all the measurements may be regarded as being derived from the mean of observers or the means of successive measures The total variation (statisticians use the "variance") can be subdivided into that between days, between observers, and between observations, or residual This will indicate whether the errors due to observers is greater or not than that due to the measures, and in consequence will give estimates of observer bias (Technically this is the analysis of variance)

The use of arithmetical means gives equal weight to all observations It could well be argued that those measurements more remote from the mean should be given less weight than those nearer, and the same would apply to observers Thus the best estimate of the mean would be obtained by a weighted summation of the results If the observations are arranged in rows and columns as described, this is known as a matrix, and finding the set of weights is equivalent to finding the first principal component of the matrix or, in psychological terminology, a general factor

The precision of a measurement can be increased by a comparatively small number of repetitions to such an extent that, even when the original measurements were comparatively crude, the final result is remarkably accurate Thus, in an experiment by Keats, Beecher, and Mosteller, the analgesic effect of 10 mg of morphine given postoperatively were compared with that of an unknown analgesic by deciding whether each injection was effective or not The quantity of unknown analgesic equivalent to 10 mg of morphine, determined by this apparently crude technique, was found, and the unknown analgesic being also morphine, the equivalent was found to be 10 8 mg of morphine This experiment shows how accurately a quantity can be measured, even though each individual measurement is made by dichotomisation into effective or non-effective, high or low, absent or present

When the measurement is near or at the critical point at which the dichotomy occurs, it will be categorised as high or low 50% of the times equally As the measurement moves above the critical point, the proportion of "high" will increase towards 100% Conversely, as it moves downwards, it will be recorded as " low " for an increasing proportion of the time This is the method used in determining the lethal dose of a drug, which is defined as that dose which will cause death in 50% of the test animals It forms the basis of most methods of biological standardisation When such data are plotted as a graph they form an S-shaped (sigmoid) curve, which is derived from the gaussian curve by adding each frequency to the previous ones

An Experiment on Clinical Judgment

A simple experiment was devised to demonstrate this method applied to the detection of cyanosis A small rubber bag was fitted to a CO_2-absorbing canister, whose other end was fitted to a rubber anæsthetic mask The bag was filled with air, and a volunteer breathed and rebreathed this air through the canister As a result the oxygen in the contained air steadily diminished until finally the volunteer became cyanosed The time required for the first appearance of cyanosis was about $1^1/_2$ minutes The experiment was then repeated, and colour photographs were taken every 10 seconds The photographs were made up into colour slides, and the first (normal), last (just detectable cyanosis), and three intermediate ones taken for the experiment Several physicians were then asked to look at the slides one at a time, presented in random order, and to say whether they showed cyanosis or not The five slides were run through ten times for each physician Each slide was then given a score, being the number of times it had been rated as cyanosed Only five observers were required to place the slides in correct order The point of the experiment is that, when the last slide is compared with the first, it is only just detectably cyanosed, therefore the intermediate slides cannot be detected, because the cyanosis they show is below threshold

Assessment of Chest Radiographs

The overwhelming majority of the pictures obtained from mass chest-radiography are normal, a few are grossly abnormal, and some show minor changes It is these that form the subject matter of the controversies on observer error We may now consider a hypothetical experiment All the radiographs are placed in order running from the obviously normal to the obviously abnormal A radiologist examines them and rates them as normal until a point is reached when he begins to be doubtful He goes on until he reaches one that is obviously abnormal, and from then on, the rest are rated as abnormal This could happen only if error could be eliminated, which is impossible

However, there is a method by which error can be reduced to below any required minimum This consists of repeating the examination of the radiographs and rating them anew The original dichotomous rating will now be changed to three categories those pictures rated as normal twice, those rated normal and abnormal once each, and those rated abnormal twice Further repetitions of the procedure will eventually produce a series in which the pictures run from those found normal every time to those found abnormal every time By analogy with the little experiment on judging cyanosis, if the observations have been repeated often enough, this order will correspond to the true order (theoretically, will tend indefinitely in that direction)

Several difficulties render this experiment impracticable The first is that " abnormality " in a chest radiograph is not a simple matter All sorts of qualities in the radiograph can separately deviate from the normal, and, in so far as these are independent, the resulting ranking orders will differ according to which has been reckoned to be the most important The attitude of the radiographer may change at each viewing, hence he will not tend towards consistency Other radiographers may differ from him in what they regard as important To a limited extent these changes between different viewings and differences between different observers can be eliminated by careful discussion between them and, above all, by the formation of a collection of standard chest radiographs illustrating the different degrees of each type of abnormality The difficulty lies here in that the clinical significance of " abnormalities " seen in chest radiographs is not yet fully understood Much further work in following up these cases has yet to be done

The point to be emphasised is that discrepancies between repeated observations and between different observers is something to be expected It can be diminished by suitable methods—i e , by the provision of standard radiographs and by the appropriate training of radiologists—but it can never be eliminated The error produced by such discrepancies can be reduced to any level by sufficiently increasing the number of times each radiograph is observed and rated

At this point a new difficulty appears—an operational problem It is true that the number of cases of lung disease missed and the number falsely diagnosed as diseased can be diminished by increasing the number of times each radograph is examined, but a radiologist can only examine a limited number of pictures For every picture that is examined a second, third, &c , time, the picture of a second, third, &c , subject cannot be examined While the radiologist is ensuring that he does not miss any cases in one district, he is missing cases in other districts because he is not there examining them In practice the gain on the one hand is not completely counterbalanced by a loss on the other It is a long and troublesome job to collect people for mass radiography in a given district It is easy and quick to examine the radiographs a second and even a third time Of course, repeated examinations of radiographs need not necessarily hold up the activities of a mass radiography unit On the other hand, there are limits to the amount of work a radiologist can do merely in examining films He needs to be refreshed by the experience of examining films of chest disease, and even by examining patients, follow up work, and so on It should not be impossible, all these problems being taken into account, including the structure of a mass radiography unit, to work out a routine that would find the maximum of cases with the resources available But operational research has not yet penetrated very far into clinical medicine

Reduction of Errors of Measurement

The simplest and traditional method of reducing errors *of measurement* is that of instrumentation Fundamentally this consists of finding a device that will magnify the changes to be measured—e g , a long pointer So far as possible, observations made through the various senses are converted into visual observations—usually a change of length This is because the perception of small changes of length is more sensitive than any other Instrumentation eliminates bias and usually reduces error to a negligible order

Unfortunately it introduces new difficulties Radiography will detect very small amounts of cardiac enlargement or very slight thickenings of lung tissue, but this sensitivity immediately raises the question of the limits of the " normal " Examples of such problems are the size of the heart, basal metabolic rate, and blood-pressure

(Of course, this problem does not arise when the difference between the normal and the abnormal is very great—e.g., phenylketonuria and galactosæmia.) When small changes can be easily detected, the problem of interpretation becomes difficult.

Universal Unit for Clinical Tests

The practising clinician is faced with this problem in another way. The increasing number of biochemical and biophysical investigations (an increase which will continue for an indefinite period) means that the clinician has to burden his memory with an increasing number of standards. As a result it is customary for pathologists to indicate in their reports what is the accepted range of the normal. An even simpler way out of this difficulty would be that of determining the distribution of the measurements in healthy people, and then giving the measurement for the individual patient in terms of the standard deviation. The clinician would then know that any measurement differing from the normal average by two standard deviations would suggest a pathological deviation, and any measure more than three standard deviations would be almost certainly pathological. This would apply to any measurement—e.g., mean corpuscular volume, alkaline phosphatase, excretion of ketosteroids, and vital capacity. The introduction of such a uniform measure would be as beneficial to clinical medicine as the introduction of money was to a barter economy. An analogy to this is the introduction of the method of measuring electrolyte concentration by milliequivalents instead of milligrammes per 100 ml. This statistical unit is so simple that it would not be rash to prophesy that it will be almost universal before the century is out.

The theory of errors has been given in the customary form, in which each measurement is regarded as consisting of a part, the "true" measurement, and another part, the "error". Since the "true" measurement cannot be obtained by any known operation it is a mythical entity. Present-day philosophy of science discards such mythical entities and confines its attention only to those results obtained by clearly defined operations. All possible measurements—e.g., of blood-pressure—are then treated as a "group", of which any one is equally representative. A series of measurements is a sample from the group, and the mean, mode, standard deviation, &c., are regarded as properties of the group.

Sampling Errors

Sometimes we measure a group of individuals to determine the characteristics of the population, of which the group is regarded as a sample. Unless all the members of the population are exactly alike as regards the measurement (in which case only one individual need be measured), different samples will give different results. This situation arises when measurement is applied to the individual patient—e.g., when a sample of blood is taken for a cell-count. In a sense this applies to any function which varies—e.g., blood-pressure and hormone concentration. A series of measurements may then be regarded as a sample from all the possible measurements. What is required from the sample is an estimate of the characteristics of the population. The accuracy of this estimate depends on the size of the sample: the bigger the sample, the more accurate is the estimate. The only way to increase the accuracy (if the sample has been obtained in the best way) is by increasing its size. Instrumentation is of no help here, because this can only diminish the error of measurement. The size of the sample that is required depends on the variability within the population and the accuracy required. If the last two are given, the first can be calculated easily.

Measurement of Complex Functions

An excess or deficiency of a hormone gives rise to changes in many functions. What is the best way of measuring the excess or deficiency? Even when the blood concentration of the hormone can be measured this would not necessarily be informative, because different individuals show different concentrations under normal conditions, and it is very rare that the normal for the individual is known. Thus it is necessary to measure the changes in the functions concerned. The easiest method of dealing with this is to measure the most important function. Unfortunately in practice this often means measuring the function that is most easily or most accurately measured.

If only one function is to be measured, the best one to choose is that which differentiates most between the normal and abnormal, taking into account the accuracy of measurement. The one measure is then an "index" of the total functions of the hormone. This is not often satisfactory, and, when one considers, for example, the history of the study of disease of the thyroid gland, one single index can be very unsatisfactory. What is required is some method of combining the results of measuring different functions to utilise all the information available. The technique for this is known and had been applied to medical problems three times.

The problem is that of finding suitable weights for the individual variables. We may regard subjects with obvious hypo-, hyper-, and eu-thyroid function as distinct groups. The measures of a sample from these groups are taken, and the dispersion matrix of these variables is calculated. This is divided into the dispersion between groups and the dispersion within groups. The former is divided by the latter, and the largest principal component of the resulting matrix gives the best weights for maximal differentiation between the groups. This is the method of multiple discriminant functions of Rao.

It is sometimes possible to measure a complex function by an appropriate complex measure. For example, if it is desired to compare two treatments for parkinsonism, it could be done by measuring the improvement of the handwriting of the patients. The handwritings of each patient in a group of (say) 20 is first ranked from the best to the worst. The first, second, up to the tenth pairs are taken, and the members of each pair allotted randomly, by tossing a coin, to one or other treatments. The patients are then given the treatments, and at the end of the trial samples of their handwriting are again taken and ranked in order. The change in rank order of one group compared with the second group would measure the difference in the effects of the treatments. To determine the reliability of the ranking it would be necessary to have the ranking done by at least two independent judges. The average of the rankings of the judges would also be more reliable.

Measurement of Subjective States

Contrary to popular belief, this is simple in theory and difficult in practice. Theoretically, the subjective state of the patient is manifested by his behaviour, and all that is needed is to find some appropriate form of behaviour. This may range from the patient's own statements about himself, in current jargon his "verbalisations", to the way he deals with such complex problems as his relations to his family, friends, work, &c. This subject of psychometrics has been under investigation for over half a century, and the literature is enormous. The practical problem is to find a suitable type of behaviour and to utilise the most appropriate method of measuring it The example given above, ranking of handwriting, illustrates one common method

Another way of measuring subjective states is to measure concomitant physiological functions For example, the response to stress of the resistance of the palmar skin, due to sweating, can be used as a measure of anxiety, so also can the electroencephalographic sensitiveness to intravenous barbiturate This is a very indirect form of measurement and is better regarded as an "index" rather than a direct measure Indexes are very much used in medicine, thus the thymol-turbidity test is an index of liver function

The trouble with such index measures is that their applicability is very limited Thus measurement of skin resistance would be useless for assessing a tranquilliser that had some ganglion-blockading effect Its relevance in patients who have cerebral damage—e g, leucotomy—has not yet been determined

Conclusions

Clinical observation has been the foundation of medicine, both in research and practice It still is It is a method which is liable to error, but so are all observations, however made In recent years much attention has been paid to "observer error", whose presence has been mistakenly assumed to invalidate the method of clinical observation Observer error can be diminished to any required degree by suitable techniques, as can any source of error of measurement The value of clinical observation in research and in clinical medicine will increase, not diminish, as the methods of handling its limitations become more widely understood and utilised The day is far distant, if it will ever be reached, when readings from machines will supersede clinical observation

I am indebted to Prof G R Hargreaves for useful advice

THE ORAL TREATMENT OF PERNICIOUS ANÆMIA

A NEW APPROACH

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SINCE the early 19th century it has been appreciated that pernicious anæmia is associated with imperfect assimilation of food The early work was clearly confirmed by Minot and Murphy in 1926 when they demonstrated that liver given by mouth can cause remission of the disease

In 1929 Castle advanced his classical hypothesis that normal human gastric juice contains a factor ("intrinsic factor") which when given by mouth with a food factor ("extrinsic factor") found in meat, will restore the blood-picture in pernicious anæmia (see Castle 1953) Castle and Minot (1936) assumed that the two factors react together to produce the hæmatologically active principle, which is then stored in the liver and other tissues

When crystalline vitamin B_{12} became available it was tested orally and found to be relatively ineffective Ungley (1952), who summarised the results of several workers, concluded that in 21 cases of pernicious anæmia daily oral doses of 5 µg or 10 µg of crystalline vitamin B_{12} either had no detectable effect or produced a trivial response When given with normal gastric juice, however, vitamin B_{12} proved to be nearly as effective as when given by injection (Berk et al 1948) This led to the idea that extrinsic factor and vitamin B_{12} are one and the same thing (Castle 1953, Berk et al 1948) Nevertheless, even in the presence of normal amounts of intrinsic factor, the intestinal absorption of vitamin B_{12} was found to be surprisingly small (Glass et al 1954) Thus an increase in the oral dose of vitamin B_{12} from 0 5 µg to 50 µg leads only to an increase in hepatic accumulation from an estimated 0 45 µg to 1 5 µg Glass et al, therefore, postulated an intramural intestinal acceptor of vitamin B_{12}, and the non-absorption of increasing doses of vitamin B_{12} was attributed to saturation of this acceptor According to present concepts, therefore, the absorption of vitamin B_{12} by the human intestine is a complex process involving the presence of a facilitating substance (intrinsic factor) and possibly an intestinal acceptor substance as well

Castle's hypothesis has led to an enormous amount of work in the search for intrinsic factor

Extensive reviews have been written by Ungley (1952) and Grasbeck (1956), but few workers can agree even on limited properties for this elusive factor Castle himself (Castle et al 1930) concluded that the intrinsic factor "is certainly not pepsin", and this view was supported by the observations of Wilkinson (1930) Ternberg and Eakin (1949) showed that vitamin B_{12} combined *stoichiometrically with a non-dialysable* substance, apoerythein, in normal gastric juice The vitamin in this combination is not available to microorganisms that need it as a *growth factor, this microbiological* technique was therefore used to assay the vitamin-B_{12}-binding principle Eakin (cited by *Hall 1950*) found the concentration of apoerythein to be low in the gastric juice of pernicious-anæmia patients, and this led to the suggestion that apoerythein was identical with intrinsic factor However, the relationship of the binding principle and intrinsic factor is by no means clear (Wijmenga et al *1954*b, *Everse et al 1953*, Williams et al *1954*, Landboe Christensen and Hoff-Jørgensen 1955, Noer 1954, Gad Andresen 1954, Baker and Mollin 1955, Beerstecher and Altgelt 1951), and vitamin B_{12} can bind itself to many substances which have no intrinsic-factor activity (Gregory and Holdsworth 1953, Hall 1950, Wijmenga et al 1954a)

Nevertheless, since the glandular mucoprotein fraction of gastric juice was found to potentiate to some degree the effect of orally administered vitamin B_{12} (Glass et al 1951) the mucoprotein nature of intrinsic factor has become widely accepted The findings of Ternberg and Eakin (1949) and Glass et al (1951) suggest that intrinsic factor has a high molecular weight, and this has led to consistent attempts to prepare vitamin-B_{12} complexes containing a protein of high molecular weight with non-diffusible properties Available commercial preparations of intrinsic factor, however, are extremely variable in their effects, and some may even inhibit the absorption of vitamin B_{12} (Williams et al 1956)

There is a growing tendency to blame species specificity for the numerous failures of intrinsic-factor preparations (Wijmenga 1957, Schwartz et al 1957) Nevertheless as *The Lancet* (1957) has pointed out, the treatment of pernicious anæmia with relatively crude preparations of hog's stomach over many years has been entirely satisfactory (see Wilkinson 1949) This editorial suggested that the cause of the failure of commercial preparations may well lie in their mode of preparation However, it occurred to us that the fault might be even more fundamental, and that an entirely new approach to the problem of the ætiology of pernicious anæmia might be desirable

There are certain well-established experimental facts Firstly, we know that vitamin B_{12} is relatively ineffective by mouth, and that, alone, it cannot mature megaloblasts in vitro (Callender and Lajtha 1951) Thus the crystalline vitamin is not the active hæmopoietic principle per se Furthermore, Robinson et al (1954) have shown that, though most of the vitamin B_{12} in crude liver extracts is bound, it is not bound to protein as such, because the active vitamin can diffuse through 'Cellophane' This seems to indicate that, in the anti-pernicious-anæmia principle, the vitamin is bound to a molecule of fairly low weight—e g, a peptide Finally, almost all forms of vitamin B_{12} available as food are bound to proteins of high molecular weight and are thus non-diffusible through cellophane and non-assimilable by microorganisms This suggested to us that a simple proteolysis may take place in the stomach, in which the "bound" protein attached to the vitamin is degraded into a peptide In this "free" form it could then be simply absorbed by diffusion through the gut wall, and thence travel to the storehouse of the liver, to be released again into the blood-stream under the action of an enzyme, erythropoietin (Fried et al 1957) as required

On this new hypothesis the inconsistencies in the action of intrinsic-factor preparations can be accounted by variation in the molecular size of the bound protein components in such mixtures Thus it is not surprising to find that vitamin B_{12}, when bound to material of high molecular weight, even though the latter be comparatively pure, does not show any activity when given orally to patients with pernicious anæmia—e g, the sow's-milk-protein complex of Gregory and Holdsworth (1953) and the purified cobalamin-protein (fiog) of Wijmenga et al (1954a), which had molecular weights of 55,000 and 70,000 respectively

Good evidence for our hypothesis would be obtained if it could be shown that a peptide derived not from an animal intestinal (intrinsic) source but from a mould or bacterial (extrinsic) source promoted the oral absorption of vitamin B_{12} (as the complex) in pernicious-anæmia patients, and, in small doses, maintained such patients in health A brief outline is given below of the isolation and properties of such a vitamin-B_{12}-peptide complex which possessed none of the properties which previously have been claimed to be necessary for absorption of the vitamin by the human intestinal tract.

Properties of the Complex

The active vitamin-B_{12}-peptide complex (H P P /1) was derived initially from fermentation of a Streptomyces mutant under standard conditions The cobalamin-peptide was released from the protein complexes within the cells and concentrated and purified by a series of steps involving ion-exchange chromatography, counter-current solvent extraction, activated-carbon treatment and ammonium-sulphate precipitation A red precipitate was finally obtained which possessed the following properties

The vitamin-B_{12} portion of the complex was estimated spectrophotometrically at 550 mμ, at which wavelength the interference of the peptide portion is very small The ratio of peptide to vitamin B_{12} on a weight basis was 6 8 1 and, assuming a 1 1 molecular ratio of vitamin to peptide, the molecular weight of the complex would be about 10,000 The true figure was probably less than this in view of the fact that the complex was dialysable and ultrafiltrable through cellophane and collodion membranes The complex did not appear to dialyse, however, against ammonium-sulphate solution under conditions which enabled the uncombined vitamin to do so

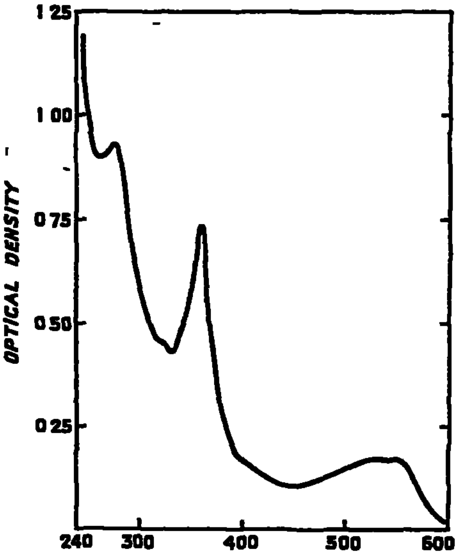


Fig 1—Absorption spectrum of H P P /1

The ultraviolet and visible absorption spectrum of H P P /1 (fig 1) possessed absorption maxima at 277 mμ, 361 mμ, and 550 mμ—i e, in the same positions as those of vitamin B_{12} The maximum at about 277 mμ was appreciably greater than the corresponding peak value for the pure vitamin

Both paper chromatography and paper electrophoresis showed the presence of only one vitamin-B_{12}-peptide Acid hydrolysis of the peptide component by 6N HCl at 100°C for twenty-four hours yielded a mixture of aminoacids, of which the following were identified by paper chromatographic separation and appropriate staining glutamic acid, aspartic acid, glycine, alanine, valine, proline, serine, threonine, arginine, cystine (or cysteine), leucine, isoleucine, phenylalanine, lysine, and histidine Methionine and hydroxyproline were not detected

Alkaline hydrolysis, followed by paper chromatography, established, with specific reagents—e g, Ehrlich's reagent—the presence of the essential amino acid tryptophane

For accuracy in administration of the tiny doses of active complex required, the vitamin content was estimated both spectrophotometrically at 550 mμ as mentioned above and by direct microbiological assay using *Ochromonas malhamensis* as the test organism That the vitamin in H P P /1 was directly assayable by organisms that require the vitamin as a growth factor shows that, according to generally accepted terminology, the vitamin was "free" and not "bound"

Maturation of Megaloblasts

Although it has been shown that folinic acid, folic acid, and vitamin B_{12} plus normal gastric juice bring about the maturation of megaloblasts in vitro, neither crystalline vitamin B_{12} nor gastric juice alone has any such effect (Callender and Lajtha 1951)

An attempt was therefore made to discover the effect of the vitamin B_{12}-peptide complex on megaloblasts in culture The technique was based upon that described by Lajtha (1952), except that Ringer's solution was used instead of Gey's, and it was found that the addition of 50 units of penicillin added to *each tube* reduced the risk of contamination The final concentration of homologous-serum in the culture medium was 80% The

18 HR CULTURES OF MEGALOBLASTIC MARROW IN 80% HOMOLOGOUS SERUM

Case no	Initial count		Cultures in					
			80% serum (8 ml)		80% serum (8 ml)+7 8 µg H P P /1 (vitamin B_{12} 1 µg)		80% serum (8 ml)+1 mg of folic acid	
	Megaloblasts %	Normoblasts %	Megaloblasts %	Normoblasts %	Megaloblasts %	Normoblasts %	Megaloblasts %	Normoblasts %
5	94	6	87	13	55	46	59	41
6	90	10	72	28	35	65	32	68

500 cells were counted on each film

results are given in the accompanying table, which shows that maturation takes place about as rapidly in the presence of vitamin-B_{12}-peptide as with folic acid in eighteen-hour cultures

Clinical Results

Six newly diagnosed cases of pernicious anæmia were treated exclusively with H P P /1 The patients were four males and two females, aged 42–72 A seventh case, which had begun to develop signs of subacute combined degeneration of the cord on treatment with another oral preparation containing intrinsic factor, is described separately below

Pernicious anæmia was diagnosed in every case by a full examination of peripheral blood, a histamine-alcohol test-meal, and biopsy of the sternal marrow (hæmoglobin 100% = 14 8 g per 100 ml)

Reticulocyte-counts were done in each case for at least three days before treatment to exclude the possibility of a coincident spontaneous remission

Dosage

As has been mentioned already, the ratio of peptide to vitamin B_{12} in H P P /1 is 6 8 1 Thus 100 µg of vitamin B_{12} is contained in 780 µg of H P P /1 For the sake of clarity the dose is given below in quantities of H P P /1 with the vitamin-B_{12} content in parentheses At no time was crystalline vitamin B_{12} given either orally or parenterally, except where specifically mentioned in case 7

Broadly speaking, treatment of pernicious anæmia is carried out in two consecutive uninterrupted stages (1) correction of the deficiency of vitamin B_{12}, and (2) maintenance of the patient on a lower dosage Ultimately the success or failure of any preparation will be judged on the second stage, for it has been shown (Blackburn et al 1955, Mooney 1956) that a good initial response to oral therapy is no guarantee of successful maintenance over long periods

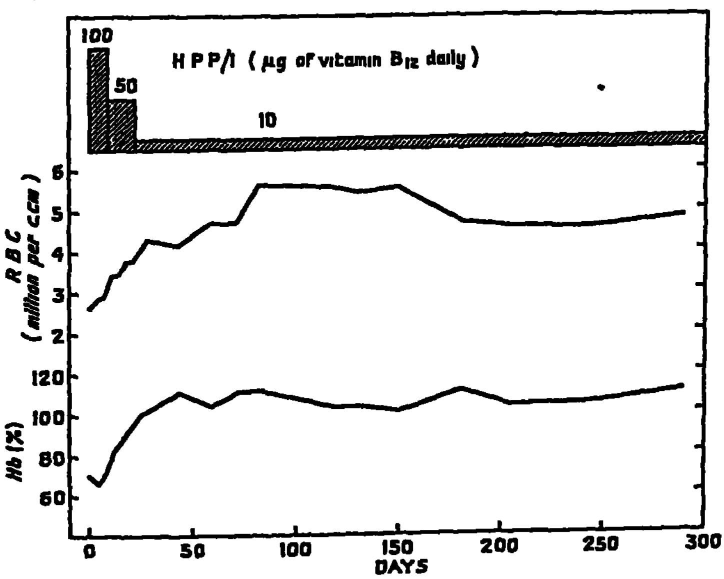


Fig 2—Case 1 (male, aged 44) blood response to oral H P P /1

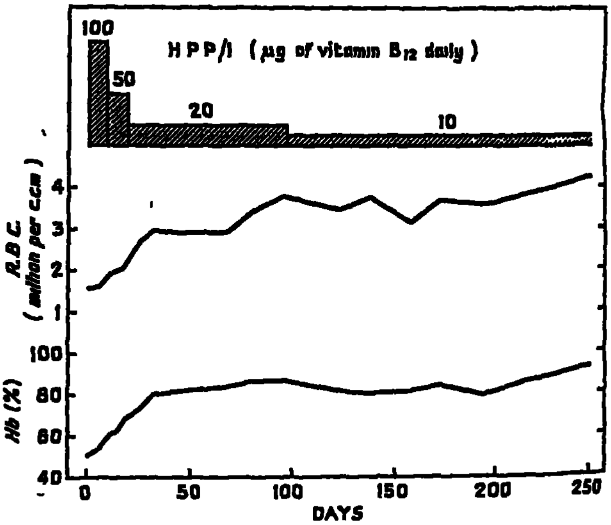


Fig 3—Case 2 (female, aged 72) blood response to oral H.P P /1

Initial dose—As it is generally agreed that the liver contains 1–2 mg of vitamin B_{12} in health, it was decided to give case 1 780 µg of H P P /1 (vitamin B_{12} 100 µg) daily for eight days, and then half that amount for fourteen more days (total dose of vitamin B_{12} 1500 µg) Dosage was varied slightly in subsequent cases but never exceeded this amount in the first three weeks' treatment

Maintenance dose—As already mentioned, Ungley (1952) considered that a daily oral dose of 5–10 µg of crystalline vitamin B_{12} had no detectable effect on the blood-picture Thus, if a patient could be maintained in health within this range of dosage, it would be reasonable to presume that the preparation was effective Accordingly 78 µg of H P P /1 (vitamin B_{12} 10 µg) was given as a daily maintenance dose in each case, except the following

Case 2 received 156 µg of H P P /1 (vitamin B_{12} 20 µg) from the 22nd to the 95th day of treatment, through fear that absorption might be impaired because she was aged 72 After the 95th day this dosage was reduced to 78 µg (vitamin B_{12}, 10 µg), and it has remained at this level up to now (246th day) without deterioration in the blood-picture

Case 3 received no treatment from the 68th to the 130th day, and his blood-picture deteriorated A single dose of 1560 µg of H P P /1

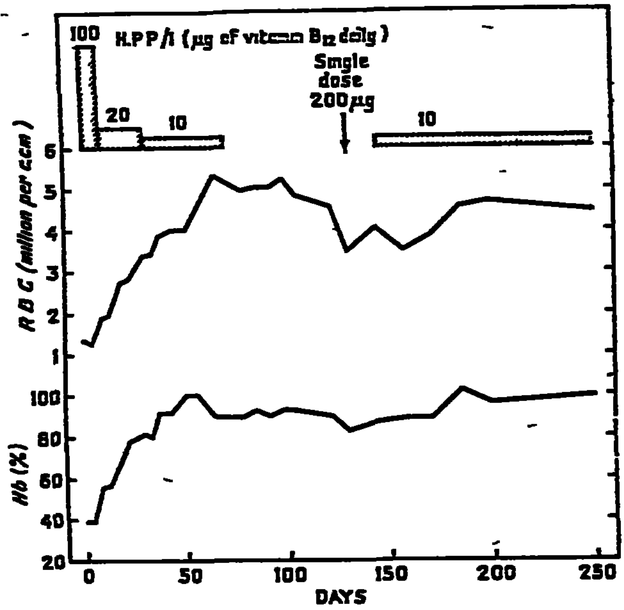


Fig 4—Case 3 (male, aged 62) blood response to oral H.P.P /1

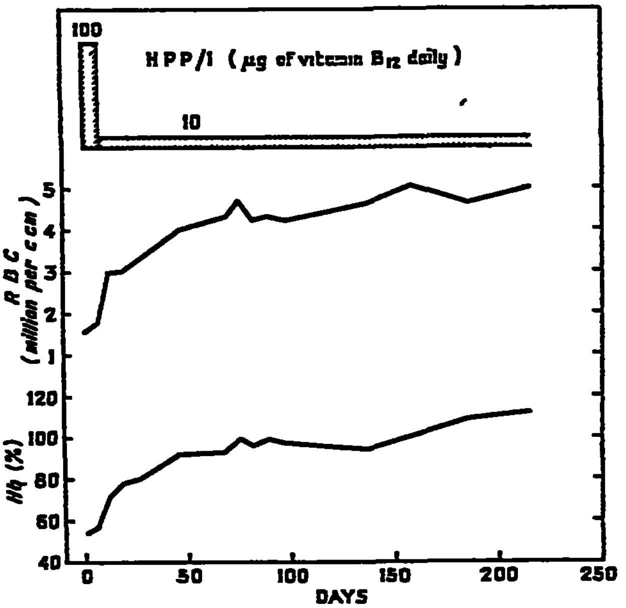


Fig 6—Case 5 (male, aged 42) blood response to oral H.P.P /1

(vitamin B_{12} 200 μg) was given on the 131st day, and from the 145th day up to now (186th day) he has received 78 μg (vitamin B_{12} 10 μg) daily

Case 6 was given weekly instead of daily doses, and from the 74th to the 123rd day she received 312 μg of H.P.P /1 each week (vitamin B_{12} 40 μg) As the blood-picture was suspected to be deteriorating (fig 7), the weekly dose was increased to 546 μg (vitamin B_{12} 70 μg) on the 124th day

Results

There was a good hæmatological and clinical response, which has been maintained in all six cases, for periods ranging from 140 to 290 days (figs 2–7) A reticulocyte crisis with maxima of 11–17% developed at about the end of the first week in every case, and the average daily increases in red cells and hæmoglobin in the first 28 days' treatment were 47,000 per c.mm. and 1·07% respectively No case up to now has developed signs either of cord deterioration or of iron deficiency

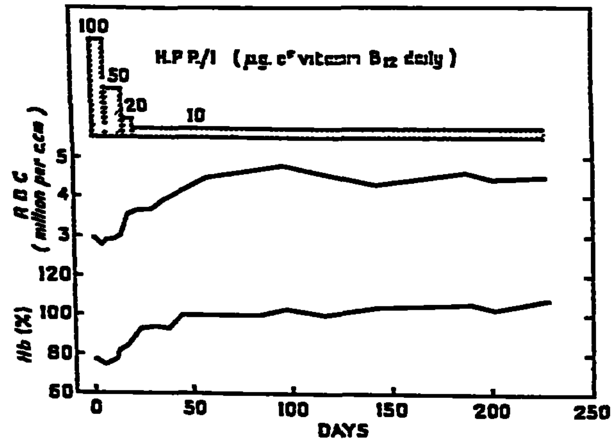


Fig 5—Case 4 (male aged 64) blood response to oral H.P.P /1

Case 7 —A woman, aged 52, had been treated with another oral preparation ('Bifacton') since pernicious anæmia had been diagnosed sixteen months previously She had responded well and had been maintained in health during this time but then began to experience difficulty in both standing up and walking, also she noticed numbness of her feet. On examination vibration sense was absent over both ankles, her knee-jerks and ankle-jerks were sluggish and her plantar reflexes equivocal. Sensation to cotton-wool was absent on the soles of both feet. Her red cells numbered 4,300,000 per c.mm. and her hæmoglobin was 94% Early subacute combined degeneration of the cord was diagnosed, and it was decided to treat her with the oral peptide complex H.P.P /1 in larger doses

Treatment.—For the first three weeks she received 2340 μg of H.P.P /1 (vitamin B_{12} 300 μg) daily and thereafter 1560 μg of H.P.P /1 (vitamin B_{12} 200 μg) daily for eight more weeks Oral treatment then had to be abandoned owing to shortage of experimental material, and the patient was given 1000 μg of parenteral crystalline vitamin B_{12} weekly

Progress—During the eleven weeks' oral therapy an unequivocal subjective improvement took place. Her walking improved, and her sensory symptoms diminished Vibration sense returned to all her malleoli except the right internal, and her reflexes showed no detectable change either way This improvement has been maintained on parenteral treatment. During twenty-four weeks' oral and parenteral treatment, her blood-count has remained essentially unaltered, and her latest red-cell count is 4,700,000 and her hæmoglobin 97%

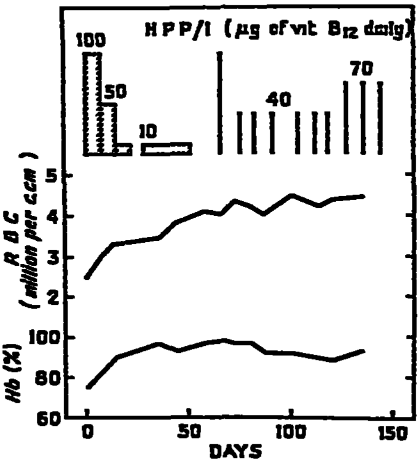


Fig 7—Case 6 (female, aged 62) blood response to oral H.P.P /1

Discussion

The current view on the ætiology of pernicious anæmia is that the absorption of the extrinsic factor (crystalline vitamin B_{12}) is facilitated by combination with the intrinsic factor Furthermore, an additional or third factor is required (Glass et al 1954) to bring about the absorption of such a large molecule in the small intestine

As crystalline vitamin B_{12} does not exist in nature but is found mostly in the "bound" form, then, if these views are correct, at some stage the crystalline vitamin must be completely detached from this protein of high molecular weight This splitting is difficult to bring about in the laboratory (Lester-Smith 1948), and whether it could occur in normal digestion in the stomach is doubtful We are certainly not aware of any reports that crystalline vitamin B_{12} has been produced in vitro from gastric secretions alone

Likewise there is no laboratory evidence that the crystalline vitamin, if it occurs as such in the stomach, combines with a specific intrinsic factor, for none has yet been isolated This does not mean that the vitamin cannot combine with the mucoproteins found in the stomach On the contrary, there is evidence (Hall 1950, Gregory and Holdsworth 1953, Wijmenga et al 1954b) that the crystalline form of the vitamin will combine readily with various proteins

There remains too the question how this non-dialysable complex is transported across the intestinal wall The third factor of Glass et al (1954) is hardly a satisfactory explanation, because it has not yet been isolated Thus, if present concepts are correct, stomach juices must be capable of freeing vitamin B_{12} from all protein adherents, furthermore, two factors—the intrinsic and the third factors—must also exist, neither of which has yet been isolated or identified

If the currently accepted ideas are correct, it should be possible to treat patients successfully by giving them orally a preparation of intrinsic factor together with a relatively small dose (say 30–45 µg) of vitamin B_{12} Although several such preparations of vitamin B_{12} and intrinsic factor have been marketed, the results have been disappointing (Blackburn et al 1955, Schwartz et al 1957) However, for reasons mentioned already, we believe that the true cause of the failure lies in something even more fundamental than this—namely, that the disease is due to a failure of simple proteolysis in the stomach In suggesting this we are largely returning to the original conception of the nature of pernicious anæmia proposed by Castle et al, who as long ago as 1930 said that it was "due to a virtual deficiency brought about, even in the presence of a diet adequate for the normal individual, by defective gastric digestion of protein as a result of the achylia gastrica"

This idea was largely discarded when it was found impossible to obtain a remission in the disease by giving pepsin and hydrochloric acid (Wilkinson 1930, Castle et al 1930), and its place has gradually been taken by the modern conception of an actual synthesis of the two factors—intrinsic and extrinsic—to form the hæmopoietic principle The isolation of crystalline vitamin B_{12} (Lester-Smith 1948, Rickes et al 1948) and its equation with the extrinsic factor (Castle 1953, Berk et al 1948) have strengthened this later view Nevertheless, as the search for the intrinsic factor has so far been unsuccessful, it cannot yet be claimed that this modern concept of the nature of pernicious anæmia is proven Indeed, from the results reported here it appears that Castle's original views may still be correct, for we have found it possible to bring about a remission in this disease by the agency of vitamin-B_{12}-peptide complex

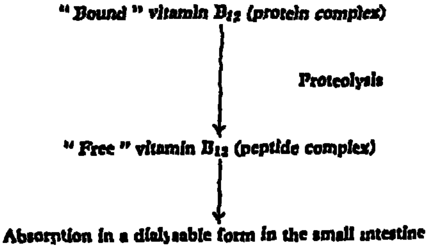
As the naturally occurring vitamin is mostly bound to protein, it seems to be an inescapable conclusion that degradation of protein must, at some stage, take place in the normal assimilation of vitamin B_{12} from food Furthermore, as no animal intrinsic factor is involved in the preparation of H P P /1 at any stage, doubt must be cast not only on its supposed rôle in pernicious anæmia but also on its existence

Before returning to Castle's original theory and restating it in the light of the results reported here, we must make clear the distinction between the confused terms "free", "bound", and crystalline vitamin B_{12}

To say that the vitamin is in the "free" form usually means that it is utilisable by those microorganisms which require it as a growth factor, and in this state it is presumably capable of diffusing through the cell wall of the organism Although the crystalline form is always "free" in this sense, the terms "crystalline" and "free" are not synonymous, nor are estimations of "free" and crystalline vitamin B_{12} in a given sample necessarily identical (Ford 1953, Hutner et al 1956) It is even possible to obtain variable estimations of "free" vitamin-B_{12} content—depending on the type of organism used—on a sample in which it is known that the amount of crystalline vitamin is constant. *Escherichia coli*, for example, gives consistently higher values of "free" vitamin-B_{12} content (Ford 1953) than does *Euglena gracilis* or *Ochromonas malhamensis* (Hutner et al 1956) As non-crystalline "free" forms of the vitamin have some peptide attached, probably this plays a variable part in the assimilation and/or utilisation of the vitamin by the test organisms

The term "bound" vitamin B_{12} means that, in this form, it is non-assimilable and non-utilisable by microorganisms It is readily converted into its "free" counterpart either by heating in an acid medium for fifteen minutes at 100°C or by proteolytic digestion Thus the conversion of "bound" into "free" vitamin B_{12} appears to entail a reduction in molecular size of the protein attached to the vitamin

Applying these terms, Castle's (1930) original theory might be stated anew as follows


"Bound" vitamin B12 (protein complex)
Proteolysis
"Free" vitamin B12 (peptide complex)
Absorption in a dialysable form in the small intestine

In other words, we believe that the complex containing a protein of high molecular weight, in which form vitamin B_{12} usually occurs in nature, is converted in the stomach into a complex containing a peptide of low molecular weight which is dialysable and assimilable by micro-organisms On this theory, extrinsic and intrinsic factors are no longer necessary, nor is the third factor of Glass, because this "free" form of the vitamin will be of a suitable size for simple absorption in the small intestine

From the clinical results presented here it is clear that patients with pernicious anæmia can be adequately maintained on oral daily doses of 10 µg of vitamin B_{12} when the latter is combined as a peptide complex derived from fermentation If these results mean anything, it must be that an intrinsic factor from animal sources, whether homologous (human) or heterologous (hog, &c) is not essential for absorption of the vitamin We believe, therefore, that intrinsic factor, as currently understood, has no real existence per se, and that the fundamental process preceding absorption of vitamin B_{12} is simply one of normal degradation or digestion of animal protein

Despite the lack of direct proof as yet, this conception of impaired proteolysis as the cause of pernicious anæmia seems to be more rational and physiological than that currently held whereby both degradation and synthesis are alleged to occur simultaneously in the same organ Furthermore, as vitamin B_{12} is usually found in the "bound" form in nature, it seems unlikely that it should be rendered "free" only to be "bound" again before absorption

In any case it is also clear from the present clinical results that H P P /1 is the most effective oral preparation yet described, because the ratio of peptide to vitamin is only 6 8 1 In other oral preparations the attached or admixed proteinaceous material (so-called "intrinsic factor") has never been less than 200 parts to 1, and usually the ratio is higher Furthermore, this preparation matured megaloblasts in vitro at about the same speed as did folic acid

Since crystalline vitamin B_{12} alone cannot bring about maturation, vitamin B_{12} seems to be more acceptable nutritionally for maturation when combined as a peptide complex and is, in this form, a closer approximation to the anti-pernicious-anæmia factor of liver than is the purified vitamin In this connection Murphy's (1954) caution that "further critical study is necessary before vitamin B_{12} is accepted as a complete substitute for either whole liver or liver extracts" is not without significance Indeed it seems likely that the vitamin might not only be absorbed but also be utilised in some similar form to this natural preparation H P P /1 Finally, we do not, on the evidence at present available, suggest that all "free" forms of the vitamin—i e, all peptide complexes—are necessarily effective clinically, but, from the results of more recent work to be published later, it appears that all active forms are probably "free"

Summary

A brief outline is given of existing theories of the causation and treatment of pernicious (Addisonian) anæmia,

Some of these have been responsible for the pursuit of intrinsic-factor preparations of high molecular weight which have not proved especially efficacious

No hypothesis so far has been able to completely and satisfactorily explain the mode of transport of vitamin B_{12} into the blood-stream

A new hypothesis is put forward that the orally active form of the vitamin is a peptide complex

Such a vitamin-B_{12}-peptide has been isolated from a fermentation of streptomyces, and it has been shown clinically to be the most effective oral preparation yet available

It is postulated that this active complex could be produced in the stomach by simple proteolysis, and that the intrinsic factor probably does not exist

It is a pleasure to acknowledge the ready cooperation we have received from Dr E T Baker-Bates and Dr G M S Ryan, who kindly allowed us to use some of their cases We thank the directors of the Distillers Co (Biochemicals) Ltd for permission to publish certain details of the method of preparation of H P P /1

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A CLINICAL TRIAL OF CHLORPROMAZINE AGAINST BARBITURATES IN TETANUS

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THE two principal current methods of controlling severe tetanus convulsions are the use of sedative drugs and neuromuscular block with artificial respiration The latter method is only suitable for special centres since the technical facilities required are considerable, moreover it has yet to be conclusively demonstrated that this method is a therapeutic advance It may ultimately prove essential for the more severe cases, but most cases of tetanus in the world will continue to be treated by simple sedation methods because the disease tends to be common where medical services are underdeveloped

We have been impressed by the prominence of polypharmacy in published reports of tetanus and by the absence of properly designed clinical trials by which individual drugs might be evaluated We compare here two sedation methods of treatment which were given concurrently, patients being allocated at random to one of two treatment groups

Design of Clinical Trial

Chlorpromazine was compared with barbiturates, and the trial was conducted on African and Indian patients admitted to the same unit at King Edward VIII Hospital, Durban

When the clinical diagnosis had been made, the patient was allocated to a treatment group by opening the next of a series of envelopes containing cards randomised between these two treatments by Dr D D Reid, of the statistical research department, London School of Hygiene and Tropical Medicine

To make sure that any differences between the two groups were due to the drug treatment only, all other treatment was standardised as far as possible Patients were also divided into two main groups, neonates and non-neonates

Standardised Treatment

Non-neonates

Procedure on admission—The patient was put on a bed and sedated with the appropriate drug, given intramuscularly or intravenously according to the severity of the tetanus, and the test dose of antitoxin was administered He was then left alone for thirty minutes, after which time he was undressed, the main doses of antitoxin were given, the wound was tended, and any necessary nursing procedures were performed

Tetanus antitoxin—All the patients received a subcutaneous test dose of 800 I U of tetanus antitoxin Thirty minutes later 100,000 I U was given intramuscularly, and thirty minutes after that all the patients aged more than 10 years were given 100,000 I U intravenously

Chemotherapy—All the patients who were aged more than 10 years were given 600,000 units, and those aged less than 10 years 300,000 units, of procaine penicillin twice daily intramuscularly during the course of the disease If clinical pneumonia developed, soluble penicillin 500,000 units was given four-hourly to patients aged more than 10 years, and the same dosage six-hourly to those aged less than 10 years

Feeding—At first a nasal or an oral stomach-tube was passed on all the patients, but later this was not done until the patient had shown himself unable to swallow Feeding was with a suitably fortified egg-and-milk mixture Intravenous feeding was undertaken when tube-feeding failed for any reason, or if the patient was dehydrated

Nursing procedures were carried out as far as possible an hour after a sedative injection

The wound was treated as it would have been if the patient had not got tetanus

Neonates

The procedure on admission was to sedate the patient as for the non-neonates No test dose of antitoxin was used, 50,000 I U was injected intramuscularly

Benethamine penicillin 300,000 units was injected intramuscularly every third day If clinical pneumonia developed this was changed to 500,000 units of soluble penicillin six-hourly

The umbilicus was cleaned with hydrogen peroxide, and merthiolate was applied to it

Feeding was by nasal or by oral tube, or intravenously if this failed At the beginning of the trial expressed breast-milk, or substitute, was given four-hourly, but this was altered to half the amount two-hourly because regurgitation developed, with its attendant risk of aspiration pneumonia Hartmann's solution was given through the stomach-tube if the child appeared dehydrated The infants were nursed with the foot of the cot raised so that bronchial and oral secretions would tend to flow out

Drug Dosage

This varied at first but was soon standardised as follows

Barbiturates

Non-neonates—Phenobarbitone sodium was the standard treatment An adult with typical moderately severe tetanus received about 200 mg intramuscularly three- to six-hourly at first, according to the frequency of convulsions When sedation was needed urgently, amylobarbitone sodium 0 25–1 00 g was given either intramuscularly or intravenously

Neonates were similarly treated with intramuscular phenobarbitone sodium 60 mg six- to eight-hourly at first, with longer intervals after the first two or three days because of the cumulative action of the drug

Chlorpromazine

Non-neonates—An adult with typical moderately severe tetanus received 100–150 mg intramuscularly four- to six hourly A total of 1 g in twenty-four hours was seldom exceeded Similar doses were given intravenously where control of convulsions was urgent At first, when patients appeared mentally distressed, promethazine, chemically close to chlorpromazine, was used in an attempt to increase sedation It was ineffective for this purpose and was soon abandoned

Neonates were similarly treated, regard being paid to their age, 20–25 mg being given four-hourly initially A total of 220 mg in twenty-four hours was seldom exceeded

In all the cases drugs were given orally only during the stage of recovery

Assessment of Severity

The severity of the tetanus was classified as follows

Mild rigidity but no reflex spasms
Moderate reflex spasms present but either mild or infrequent
Severe frequent severe reflex spasms

Results

Tables I and II compared the two treatment groups Table III gives the mortality figures Table IV gives the complication-rates and feeding routes Table V gives the principal prognostic criteria of tetanus, the period of onset—the time from the first symptom to the first generalised reflex spasm (Cole 1940)—and the incubation period

Discussion

Choice of Drugs

Barbiturates were chosen because they are well known to arrest tetanus convulsions although often at the price of unconsciousness and respiratory depression

Chlorpromazine was chosen because it was, at the time of the trial, the most potent of a range of drugs assayed on local tetanus in rabbits (D R Laurence and R A Webster, unpublished) In addition it had been found possible to arrest clinical tetanus spasms by its sole use (Kelly and Laurence 1956, Laurence 1957)

TABLE I—COMPARISON OF GROUPS, NON-NEONATES

—	Chlorpromazine treated	Barbiturate treated
No of cases	23	21
Average age (yr)	18	22 5
Race		
African	16	12
Indian	7	9
Sex		
Male	15	13
Female	8	8
Average incubation period (days)	15*	10 5
Average period of onset (hr)	32	30 5
Severity		
Severe	15	13
Moderate	7	6
Mild	1	2
Site of wound		
Leg	12	12
Scalp	3	2
Arm	3	1
Uterus	0	1
No wound found	5	5
Clinical sepsis present on admission	7	9

* This figure is high because 1 case had an apparent incubation period of 60 days

TABLE II—COMPARISON OF GROUPS, NEONATES

—	Chlorpromazine treated	Barbiturate treated
No of cases	14	17
Average age (days)	8	7·5
Race		
African	13	14
Indian	1	3
Sex		
Male	6	8
Female	8	9
Average incubation period (days)	7	5·5
Average period of onset (hr)	18	24
Severity		
Severe	14	17
Moderate	0	0
Mild	0	0
Site of wound (umbilicus)	14	17
Clinical sepsis present on admission	13	17

Division of Patients

Because of the high mortality-rate anticipated and feeding problems, neonates were given a modified standard treatment and the results assessed separately from the non-neontal patients. There were not enough children to make it useful to separate them as a special group.

Procedure on Admission

Immediate sedation followed by a period of quietude was considered essential so that such necessary procedures as the main antitoxin doses and tending the wound would provoke severe convulsions.

Antitoxin Dosage

This was standardised at a high level so that the same dose would be suitable for even the most severe cases. One patient, who had trodden on a nail, was found post mortem to have, deep to the tendons on the sole of his foot, an abscess which had given no signs of its presence during life. Since it is possible that this was a source of huge amounts of toxin, the antitoxin administered may have been inadequate in this case. No hypersensitivity reactions occurred.

TABLE III—DEATHS

—	Chlorpromazine treated	Barbiturate treated
Non-neonates		
No of cases	23	21
No of deaths	10 (*43%*)	11 (*52%*)
Deaths among patients surviving more than 24 hr in hospital	8 (*38%*)	8 (*44%*)
Neonates		
No of cases	14	17
No of deaths	13 (*93%*)	12 (*71%*)
Deaths among patients surviving more than 24 hr in hospital	10 (*91%*)	11 (*69%*)

Feeding

Previous experience had taught us that it is better to pass a stomach-tube unnecessarily than to leave it too late. Once difficulty in swallowing has developed, passage of the tube may soon become very difficult indeed, the disturbance of the patient is tremendous, and the tube is liable to enter the trachea. The ability of half of the non-neonates treated with chlorpromazine to swallow successfully (table IV) was striking, and we attribute this to the drug. Of the barbiturate group 30% required intravenous feeding because a stomach-tube could not be passed; this contrasts with the chlorpromazine group, where none needed intravenous therapy because of failure to pass a tube. All the neonates were fed by stomach-tube except 1 in the barbiturate group, who was fed intravenously because a tube could not be passed.

Bronchial and Oral Secretions

These were encouraged to flow out by nursing all the patients tilted head down. Oral suction was occasionally used, tracheal suction never.

General Nursing

Disturbance of the patient was avoided as much as possible. A specially allotted nurse was usually available, but she often had to care for as many as four seriously ill patients at a time. At other times this was done by an untrained nursing aide.

Oxygen

Oxygen was not used in the non-neonates, because cyanosis was not a feature except immediately after convulsions, and it never persisted after respiration had been re-established. Attempts were made to give oxygen to the neonates by nasal tube, but this provoked such vigorous spasms that it was abandoned. Oxygen tents and incubators were not available, and it is uncertain whether they would have been useful.

TABLE IV—COMPLICATIONS AND FEEDING

—	Chlorpromazine treated		Barbiturate treated	
	Survived	Died	Survived	Died
Non-neonates	13	10	10	11
Pulmonary complications				
Present on admission	3	2	1	2
Developed in hospital	0	2	2	7
Other important complications (excluding wound)	6	7	7	8
Feeding				
Oral	7	5	5	0
Tube	6	2	4	2
Intravenous	0	2	1	6
Not fed (died too soon)	0	1	0	3
Neonates	1	13	5	12
Pulmonary complications				
Present on admission	0	1	0	1
Developed in hospital	1	7	1	8
Other important complications	1	5	5	7
Feeding				
Oral	0	0	0	0
Tube	1	12	5	11
Intravenous	0	0	0	1
Not fed (died too soon)	0	1	0	0

Chlorpromazine

This was usually given intramuscularly. It is intensely irritant and, although this was not a problem in the non-neonates, the neonates developed extensive induration of their muscles, which must have been painful and tended to provoke spasms. Histological study after death showed necrosis of muscle at the injection sites. An attempt was made to mitigate this by diluting the solution (25 mg. or 50 mg. per ml.) with at least its own volume of saline solution, but this probably made no difference.

TABLE V—PRINCIPAL PROGNOSTIC CRITERIA

Treatment group	Average period of onset (hr)	Average incubation period (days)
Non-neonates		
Chlorpromazine		
Deaths	23	15 (6/10)*
Survivals	41	15 (11/13)*
Barbiturates		
Deaths	13	11 (9/11)*
Survivals	48	10 (8/10)*
Neonates		
Chlorpromazine		
Deaths	9	6
Survivals	27	8
Barbiturates		
Deaths	10	5
Survivals	38	6

* These figures indicate the number of cases in which it was known—i.e., 6/10 = 6 out of 10 cases.

In neonates the incubation period was presumed to start at birth.

In 1 case very severe generalised convulsions were not arrested by 500 mg of chlorpromazine given intravenously In all the other cases the convulsions were controlled by smaller doses and were not usually thought to be the primary cause of death It is difficult to decide exactly what causes death in tetanus

3 non-neonates became confused, and 1 of them had a parkinsonian tremor This was attributed to overdosage of chlorpromazine 2 of these patients, who died, were receiving more than 1 g of chlorpromazine daily The 3rd, with confusion plus tremor, was receiving 600 mg daily and recovered A neonate died on the eleventh day after receiving chlorpromazine 360 mg daily for several days His tetanus was controlled At necropsy only pulmonary œdema was found, and death was thought to be due to chlorpromazine poisoning In 1 patient (not included in this trial) intravenous amylobarbitone 500 mg, followed by the same dose half an hour later, did not control the spasms for more than fifteen minutes after each injection An intravenous injection of 100 mg of chlorpromazine thirty minutes after the second dose of amylobarbitone was followed by rapid relaxation The patient became comatose in ten minutes It was more than twelve hours before the spasms recurred, and they remained mild for several more hours This was considered to be due to the well-known potentiating effect of chlorpromazine on barbiturates

Clinically chlorpromazine relaxes tetanus spasm more effectively than do barbiturates, unless the latter are given in large enough dose to cause loss of consciousness Retention of consciousness and absence of clinical respiratory depression seem to be an advantage

Barbiturates

The amylobarbitone-phenobarbitone combination was easily manipulated in the non-neonates, but we felt that equally good results could have been obtained with amylobarbitone alone In the neonates phenobarbitone proved to be cumulative, and after the first two or three days as little as 30 mg daily sometimes sufficed to keep the child well sedated There is no doubt that a few neonates were oversedated, and that this contributed to death, but it would give a false impression of accuracy to give a figure for the incidence of this To find the smallest dose adequate to control the convulsions without causing respiratory depression is not easy, and sometimes the latter must be accepted as the price of freedom from convulsions Prolonged use of phenobarbitone in neonates may be undesirable because of its slow metabolism and excretion Amylobarbitone may well be the preferable drug

Prophylactic Antitoxin

A male African, aged 45, had 1500 I U of antitoxin given after multiple stab wounds He had an incubation period of fourteen days and no premonitory symptoms He was treated with barbiturates and died after two days

Comparison of Treatment Groups

The more important features of the two treatment groups are compared in tables I and II There are no statistically significant differences

Mortality-rates (*Table III*)

The trial was stopped at a total of 75 cases because no statistically significant differences had emerged and because each treatment had its disadvantages The high death-rate in the neonate chlorpromazine group may well be due to chlorpromazine poisoning A second trial of chlorpromazine against a mixture of barbiturates and chlorpromazine was begun and will be reported later

Since some patients survived only a few hours after admission to hospital and can hardly be said to have had any treatment, the death-rate of those surviving more than twenty-four hours in hospital is given separately

Complications and Feeding (*Table IV*)

Necropsies were made on all those who died, except 1, by the department of pathology of the University of Natal and by the pathologists of the Government mortuary The figures for complications are therefore more accurate for the patients who died than for those who recovered Pneumonia was suspected before death in a few patients, usually neonates, whose lungs were found at necropsy to be uninfected Chest radiographs were not taken during the stage of severe tetanus

Although not reaching the conventional level of statistical significance, the absence of pulmonary complications in the chlorpromazine group of non-neonates is striking and may be of importance Furthermore stomach-tubes were passed with greater ease in the chlorpromazine than in the barbiturate group The chlorpromazine group of non-neonates needed a tube less often, and patients were able to swallow throughout the illness more often than the barbiturate group

The "other important complications" included drug overdosage, laryngospasm, malnutrition, fractured vertebræ, bilharziasis, pulmonary tuberculosis, accidental overhydration, dagga (*Cannabis indica*) addiction, acute pyelitis, abortion, fractured skull with epilepsy, gonococcal ophthalmia, prematurity, changing from breast to artificial milk during the illness, cerebral thrombosis, jaundice, and severe nasal sepsis It is impossible to assess the part some of these played in the patients who died Convulsions are not the immediate cause of death in tetanus as often as is commonly assumed Necropsy is not so helpful as could be hoped It is possible that direct action of the toxin on the vasomotor and respiratory centres is the most important factor

Tracheotomy

It is generally agreed that pulmonary complications are an important cause of death in tetanus, and in this trial, in which no tracheotomies were done, the development of pneumonia, after treatment had begun, was common in all except the chlorpromazine-treated non-neonates, among whom, despite oral feeding in half the cases and the use of a stomach-tube in most of the remainder, there were only two cases of pneumonia after admission to hospital

There were three reasons why it was decided only to do tracheotomy on patients if and when conclusive indications appeared

(1) There is no proof that tracheotomy improves the prognosis, whereas it certainly complicates management

(2) It carries its own complications Forbes and Auld (1955) did tracheotomy on 10 patients, in 7 of whom mediastinal emphysema, atelectasis, or pneumonia developed 5 of their patients required bronchoscopy, 3 of them more than once

(3) The prospect of doing tracheotomy on seriously ill children, often aged less than 1 week, was sufficiently alarming to be avoided in the absence of conclusive evidence of its value

Looking back over the series we feel that tracheotomy would have been desirable at least in cases where laryngospasm developed, but these were few (3) and unpredictable The suggestion that tracheotomy is obligatory in patients fed orally or by stomach-tube is certainly reasonable, and it is hoped to obtain evidence on this matter in a later trial The tendency of neonates to regurgitate probably renders tracheotomy (and intravenous feeding) especially necessary in that group We are disinclined to accept this indication absolutely because tetanus is common in areas where technical facilities are comparatively few, and overloading the essential schedule of treatment with conceivably unnecessary tracheotomy is to be, avoided if possible Routine intravenous feeding is even more impracticable The practice of routine tracheotomy in centres specially experienced in treating respiratory disease and poliomyelitis, and where tetanus is only occasionally met with, is as justified as routine tracheotomy in this series would have been unjustified

Laryngospasm

Severe laryngospasm provoked by stimulation (passage of a nasal tube or an injection) developed in 3 cases, all in the barbiturate non-neonate group 2 of the patients died, apparently as a result In both of these sedation was manifestly inadequate, but the surviving patient appeared to have been well sedated

Sudden Arrest of Respiration

This happened thrice in 1 non-neonate (an Indian male aged 7 years), and manual artificial respiration was followed by return of spontaneous respiration in a few minutes on the first two occasions The third occasion was fatal

Similar repeated respiratory failure developed in 3 neonates who died and in 1 who survived Since neither respirators suitable for neonates nor the staff to manage them were available, the question of whether to use continuous artificial respiration with or without neuromuscular block did not arise It is impossible to say how often patients who died would have started breathing again, at least temporarily, if someone had been at hand to give artificial respiration Of the 5 patients who had more than one attack of respiratory failure, 4 were treated with barbiturates and 1 with chlorpromazine Respiratory stimulants (nikethamide, bemegride) were given as well as artificial respiration, without apparently making any difference Periods of gasping respiration were common before death in the neonates

Prognostic Criteria (*Table V*)

The period of onset is the most important criterion of prognosis The incubation period is unreliable because the time of wounding (or birth) from which it is calculated may not be the time of infection, and because there are patients in whom no attributable wound is found It is usually considered that a period of onset of less than forty-eight hours carries a serious prognosis In all our groups the average period of onset was forty-eight hours or less, indicating that the tetanus was usually very severe Some patients denied any symptoms before the onset of reflex spasms However, death and survival were by no means closely related to the duration of the period of onset 9 non-neonates with periods of onset of less than twenty-four hours survived It is not rare to read reports of a few, or even single, cases of tetanus in which it is stated that the patient would have died because of a short incubation period or period of onset, and that survival must be attributed to the treatment given Such claims are unacceptable because these prognostic criteria are only general guides and give no certain information on the outcome of an individual case Tetanus does not differ from other infections in that properly designed clinical trials are necessary if the value of a treatment is to be determined with the greatest economy of lives

Comparisons of mortality figures between one published series of tetanus and another are also liable to be misleading because, for example, the quality of the nursing may well be more important than the drugs used Reports of single cases are only of value in describing new techniques, they give no conclusive proof of the efficacy of a treatment There have been reports of administration of chlorpromazine to tetanus patients dating from its introduction into anæsthetic practice in combination with pethidine and promethazine The specific tetanus anticonvulsant action does not seem to have been suspected at first, with the result that small doses were given and chlorpromazine was never used alone, which is the only way of evaluating it In fact phenothiazine compounds are the most potent available substances which may arrest tetanus spasms without significantly depressing respiration or consciousness (D R Laurence and R A Webster, unpublished) It remains to be seen what part these drugs will play in the treatment of tetanus, because it is by no means certain that mere control of convulsions together with prevention of pneumonia will ensure survival in all cases

Summary

A clinical trial was made on 75 tetanus patients allotted at random to two treatments practised concurrently

Chlorpromazine and barbiturates, when used as described, cause no statistically significant difference in the outcome of tetanus

Chlorpromazine is easier to manage than barbiturates because it controls tetanus convulsions without causing loss of consciousness or clinically noticeable respiratory depression.

We thank Dr D D Reid for advice on the design of the clinical trial as well as for preparing the envelopes with which the patients were randomised, Dr S Disler, medical superintendent, King Edward VIII Hospital, Durban, for facilities for the clinical trial, and Maybaker Pty for a gift of chlorpromazine Dr D R Laurence visited the department of medicine of the University of Natal in 1956 with a grant from the Wellcome Trust

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EFFECT OF CHLORPROMAZINE ON MUSCLE SPASM IN HUMAN TETANUS

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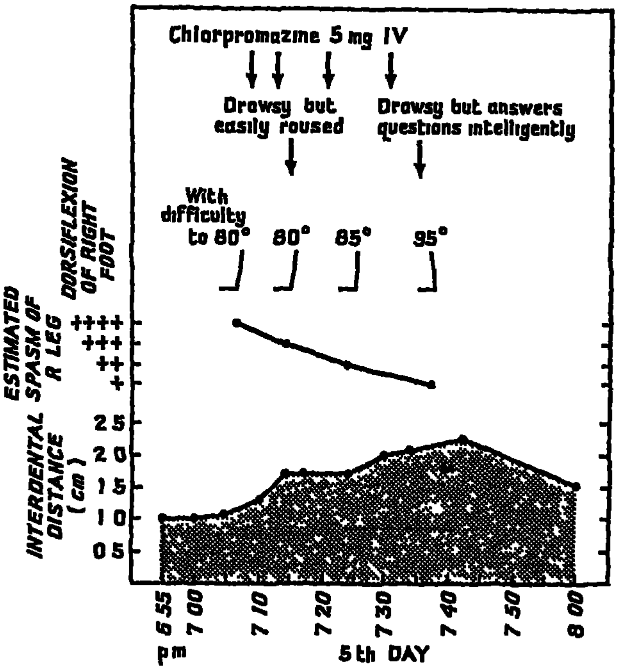
TETANUS may be general, local, or a combination of both In man local tetanus is relatively uncommon, but it is readily produced experimentally Hougs and Andersen (1954) and Kelly and Laurence (1956) studied the effect of drugs of possible therapeutic value on the muscle spasm of local tetanus in the rabbit Since chlorpromazine showed promise it was given to patients with general tetanus Kelly and Laurence, in their successful treatment of a child, used it alone to combat the spasms, they discuss its probable mode of action Other workers have combined chlorpromazine with depressants of the central nervous system and with neuromuscular blocking agents, but opinion differs about the value of chlorpromazine



Effect of intravenous chlorpromazine on trismus and muscle spasm of right leg (See text for explanation of terms and symbols used in diagram)

I report here a case of tetanus with mainly local manifestations because chlorpromazine immediately and unequivocally reduced the muscle spasm

Case-report

A girl, aged 11 years, injured her foot on some old wood on Feb 2, 1957 The wound suppurated, and on Feb 17 trismus developed Late on Feb 18 she was admitted to hospital, complaining only of trismus and hunger She denied stiffness of either leg or any other symptom Her previous health had been excellent, and she had not been actively or passively immunised against tetanus

On examination she looked well and was apyrexial, but could not separate her teeth more than 1 cm —attempts to do so decreased this distance There was a suppurating puncture wound on the medial side of her right sole Muscle spasm held her right foot in inversion and plantar flexion, and her right knee was flexed Both knee- and ankle-jerks were exaggerated, with poorly sustained clonus, more especially on the right Her left leg was otherwise normal Her arm, abdominal, and plantar reflexes were normal, and the rest of the clinical examination was negative

Treatment and Progress

Treatment began with antitetanus serum, wound toilet under general anæsthesia, penicillin, and intravenous infusion Sodium phenobarbitone gr, 2 at 2 A M and gr 3 at 7 A M was given intramuscularly, and phenobarbitone gr 1 was given orally thrice during that day The patient became deeply sedated though rousable for fluid feeds, but by evening the trismus and spasm of her right leg had worsened Phenobarbitone was stopped and a trial of chlorpromazine started, the interdental distance—i e , the distance in centimetres between the edges of the incisors when the patient opened her mouth as widely as possible—being used as a measure of its efficacy

The first dose (at 6 P M on third day of illness) had a dramatic effect Before treatment with chlorpromazine the interdental distance had been 1 cm and the knee-jerks exaggerated (examination was limited because it made the spasm worse) Immediately after the slow intravenous injection of chlorpromazine 20 mg the interdental distance was 2 5 cm , *increasing after six minutes to 3 cm Tendon-reflexes and limb* spasm disappeared, and the patient became sleepier but still easily rousable Her respirations, pulse-rate, and blood pressure were unchanged At midnight she was rousable, but her jaw and right leg were still relaxed and knee-jerks absent, but by 9 A M trismus, spasm of her right leg, and exaggeration of her knee-jerks had returned Liquids only had been taken that morning Chlorpromazine 10 mg increased the interdental distance to 1 9 cm and made the patient drowsy At 2 P M the interdental distance was 1 5 cm , the reflexes were normal, and she had just eaten a three-course lunch By 4 P M trismus, &c , had returned, but chlorpromazine 5 mg reduced it as before It had been noted that day that, if one tried to dorsiflex her right foot, spasm worsened and opposed the movement (response to stretch), but by 10 P M light touch on her right foot elicited a violent painless convulsive "withdrawal" movement characterised not only by contraction of the inverter and plantar flexor muscles of the foot and of the hamstring muscles but also by palpable contraction of the quadriceps muscle The patient had not noticed this convulsive movement occurring spontaneously but she felt the limb "stiff" for the first time that day The severity of limb spasm could now be recorded in two ways (1) the estimated angle from the horizontal to which the right foot could be dorsiflexed (the left foot could be dorsiflexed to 95°), and (2) the degree of reflex spasm, which was arbitrarily graded as follows (in the diagram the symbols are shown vertically)

++++	*Violent "withdrawal" spasm (as described above) on lightly touching the toes of the right foot*
+++	*Similar spasm elicited if foot touched more firmly*
++	Plantar flexion present and increased on dorsiflexing foot
+	Increased tone compared with left limb

In the accompanying figure the effect of intravenous chlorpromazine on trismus and limb spasm is shown diagrammatically *This pattern of response* is typical of that regularly obtained during the fifth and sixth days of the disease Chlorpromazine 20 mg *reduced* trismus *for five* or six hours and limb spasm for a variable but shorter period

On the sixth day thiopentone 50 mg , given two hours after chlorpromazine 20 mg , reduced considerably further, *for a few minutes, trismus and limb spasm, though* consciousness was unimpaired—the child was eating lunch five minutes later This effect was confirmed twice

On the seventh day substitution of chlorpromazine 50 mg six-hourly *for intravenous chlorpromazine* was begun, and treatment with phenobarbitone (gr 1 six-hourly) was started *again When phenobarbitone* was withheld on the tenth day, the patient's improvement continued for twenty-four hours, then the spasm increased, requiring twice as much chlorpromazine to control it Until the thirteenth day any disturbance, such as the entry of students or visitors, had increased the trismus and limb spasm Since on that day it did not, and since the interdental distance was 3 cm , with no appreciable limb spasm, chlorpromazine was withheld, and the child was moved to the main ward The spasm immediately returned, especially that of the limb, therefore treatment with chlorpromazine 100 mg six-hourly was resumed for forty-eight hours, when the spasm again became minimal On the seventeenth day the patient got up, but the increased tone in the calf caused her to walk in equinus for two days When she was discharged on the nineteenth day, her interdental distance was 2 8 cm Six weeks later it was 4 3 cm and she was clinically normal

During treatment there was no complication, and frequent examinations of the blood and urine showed no evidence of jaundice or of depression of the bone-marrow

Discussion

In this child the limitation of muscle spasm to the jaw and one leg facilitated study of the effect on it of drugs and disturbance I do not suggest that the methods described will be useful for assessing ordinary clinical response, because usually it is undesirable to stimulate the patient in this way This child had an excellent prognosis, and recovery was probable even without any sedative or antispasmodic therapy Nevertheless there is no doubt that chlorpromazine modified the spasm and, by relieving her trismus, enabled her to eat a normal diet, and she remained conscious Full phenobarbitone sedation had provided neither advantage A further, though hypothetical, benefit might have been the minimising of contracture—a recognised sequel to local tetanus (Millard 1954) In experimental local tetanus the early reflex or "hypertonic" contraction, which can be abolished by section of the nerve, deep anæsthesia, curarisation, &c, is succeeded in four or five days by "myostatic contracture" This is unaffected by any of the measures mentioned above, but may recover spontaneously in from four to eight weeks (Ranson and Ranson 1929) Its cause is unknown, but, since it is always preceded by reflex spasm, perhaps the spasm in some way damages the muscle, leading to "myostatic contracture" If this were so, the reduction of early spasm by suitable drugs, as was done intermittently in the present case, might minimise subsequent contracture and so shorten disability In this child the time taken for clinical recovery of the muscles compares favourably with the much longer periods—up to several months—reported by some workers (see Millard 1954)

The effect of the initial dose of chlorpromazine, given during deep phenobarbitone sedation, was never matched by subsequent and larger doses, and thiopentone, given during the period of action of chlorpromazine, temporarily but considerably increased the interdental distance These facts suggest that a combination of phenobarbitone and chlorpromazine, as used by Cole and Robertson (1955), might be superior to chlorpromazine alone This theory was not tested by parenteral dosage, but the response to the combination given orally seemed to favour it No conclusion however, was reached

Summary

An unusual case of tetanus is reported in which it was possible to measure roughly the effect of drugs and disturbance on spasm

Full sedative doses of phenobarbitone did not relieve the spasm, but chlorpromazine did

I am grateful to Prof D M Douglas for allowing me to assist in the treatment of his patient and to publish this case I was in receipt of a grant from the Scottish Hospital Endowment Research Trust

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"A young lady keeps her bed for two or three years for an affection of the hip, and is seen by all the leading men in London One day the clergyman walks in, prays over her, and she gets up and walks The case is reported in all the religious journals as a miracle, whereupon the doctors all join in declaring that the case was one of hysteria, and that there was nothing the matter with her Then, I would ask, why was that girl subjected to local treatment and to the infliction of physic every day for years? Why did not the doctors do what the parson did?"—SIR SAMUEL WILKS *Lectures on Diseases of the Nervous System* London, 1878, p 374

ISOLATION OF TRACHOMA VIRUS IN EMBRYONATE EGGS

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THE laboratory cultivation of trachoma virus has long been attempted by different workers, but claims to success (Machiavello 1944, Stewart and Badir 1950, Poleff 1950, 1954) have not been confirmed The expert committee on trachoma of the World Health Organisation (1956) was not convinced that the cultivation of the virus had been achieved in series or in quantity

T'ang et al (1957), however, in China, made three isolations of a virus from patients with trachoma by inoculating conjunctival material into the yolk sacs of 6–8-day embryonate eggs The egg-cultured virus produced a follicular conjunctivitis in rhesus monkeys, in one instance with inclusion bodies Various animal and other tests distinguished the virus from hitherto described viruses, in particular those of psittacosis and lymphogranuloma, which it resembled morphologically

Our preliminary results recorded here have confirmed the findings of the Chinese workers with the isolation of a morphologically and serologically similar virus from patients with trachoma in the Gambia, and have identified it as the causal agent of trachoma by inoculation of a human subject

The Chinese Virus

Dr T'ang kindly supplied us with freeze-dried samples of his strains of virus, which were brought from Peking in September, 1957, by Prof E T C Spooner Strains TE8 (13th egg passage) and TE55 (8th egg passage) were revived without difficulty in the yolk sacs of 8-day embryonate eggs incubated at 35°C as recommended by T'ang In general we confirmed the original morphological description of the virus, its lethal effect on chick embryos, however, was not so constant as reported by T'ang Both strains have now undergone 6 egg passages at the Lister Institute After 2 egg passages three young rhesus monkeys were inoculated with strain TE55 by the conjunctival route Two monkeys developed follicles in the upper fornix of the inoculated eye on the 8th and 20th days The follicles persisted for about 8 weeks, the control eyes remaining normal throughout Although cytoplasmic inclusions were occasionally found in scrapings from the infected conjunctivæ they were never typical of the classical Halberstaedter-Prowazek (1907) bodies

Isolation of Virus from Trachoma Patients in the Gambia

Our viruses were isolated by methods similar to those of T'ang et al (1957) To avoid any possibility of confusion, live Chinese virus was never sent to the West African laboratory.

Method of Isolation

Material was taken from patients in whom typical trachoma inclusions had recently been found The upper lid was everted and rubbed with a swab moistened with 10% broth-saline The swab was placed in broth-saline 0 5 ml which contained streptomycin 500 µg to inhibit bacterial contaminants, and held for an hour at 4°C (Penicillin was not used, because the Chinese workers reported it to be antiviral) The fluid, including that squeezed from the swab, was used to inoculate 2-day, 5-day, or 6-day embryonate eggs by the yolk-sac route Viruses closely resembling the Chinese strains were isolated from 10 trachoma patients They were freeze-dried as crude yolk-sac homogenates in 2 5% peptone and sent by air-mail to the Lister Institute The following notes illustrate a typical isolation

Case 1.—A Mandingo girl, aged 8 years, was examined on May 20, 1957, with the slit-lamp by Mr M Gilkes, who reported trachoma III, follicles+, papillæ+++, scarring+, well-developed 5-mm pannus, and slight corneal infiltration in advance of pannus No inclusions were found in conjunctival scrapings

On Nov 20 she was Frei-test negative after 48 hours

On Nov 27 inclusions were found in conjunctival scrapings, and conjunctival material was injected into two eggs

On Dec 6 one embryo died A yolk-sac smear stained by Castañeda's method showed numerous elementary bodies

This strain of virus, designated G1, was passaged four times in eggs before dispatch to the Lister Institute (see table) It has now undergone ten yolk-sac passages made by inoculating the yolk sacs of 6–8-day embryos with 0 25 ml of 20% suspensions of infected yolk sac in 10% broth-saline

INITIAL EGG PASSAGES OF STRAIN G1

Passage no	No of embryos inoculated	No of specific deaths	Days after inoculation on which embryos died
1	2	1	9
2	6	5	8, 8, 8, 9, 9
3	7	5	4, 4, 4, 4, 6
4	9	8	4, 4, 5, 5, 6, 6, 6, 6

Morphology and Staining Reactions

Morphologically the Chinese and the Gambian strains of virus are very similar Smears from infected yolk sacs contained numerous elementary bodies staining red by Machiavello's method, and blue with Castañeda stain Giemsa-stained particles ranged in size from 0 2 to 0 5 μ, the smaller staining pink and the larger blue or purple Most forms were round, and some slightly elongated They occurred singly or in aggregates, mostly extracellularly Some intracellular forms were present, usually as large purple granules, sometimes as big as 1 μ in diameter In one yolk sac infected with a Gambian virus numerous yolk cells were packed with virus particles which stained characteristically with Giemsa and with Castañeda, in this instance the embryo survived, and the yolk sac was removed shortly before hatching was due

Electron Microscopy

Viruses from the 16th egg passage of Chinese strain TE8 and from the 8th egg passage of strain G1 were purified by differential centrifugation and treatment with 'Arcton 63' (1 1 2 trichloro 1 2 2 trifluoroethane) by a method similar to that of Gessler et al (1956)

Electron microscopy revealed objects strikingly similar to the elementary bodies of other members of the *Chlamydozoaceæ* (Rake 1947, Heinmets and Golub 1948, Gaylord 1954) In the electron micrographs (fig 1a and b) the collapsed desiccated bodies measure 0 3–0 4 μ Rather larger forms, not shown here, were also seen No such bodies were found in an extract of normal yolk sac similarly prepared, and it is highly probable that they represent the virus

Action of Virus on Chick Embryos

Although a heavy inoculum of virus usually killed embryos in 4–11 days, this was not the rule, and living embryos examined just before hatching sometimes had numerous elementary bodies in the yolk sac Embryos dying after infection usually, but not always, had petechial hæmorrhages in the skin and intense congestion of the liver and kidneys but apparently a normal spleen In only 2 of 12 embryos dying after infection with strain TE8 were virus-like particles found in smears of the viscera in one they were present in the skin, brain, spleen, liver, lung, and kidney, but in the other only in the skin

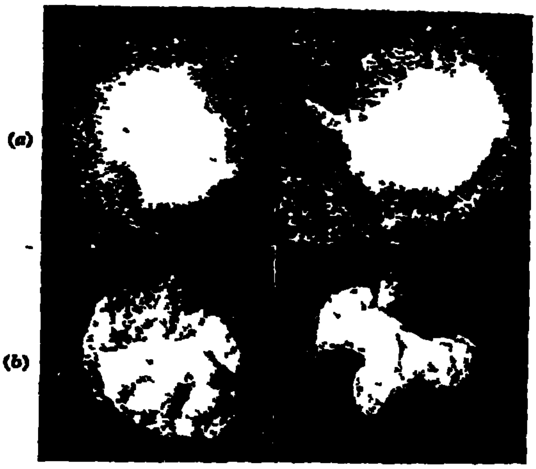


Fig 1—Electron micrographs (×67,000) of virus-like bodies in purified suspensions of (a) strain TE8 and (b) strain G1

Serological Investigations

The serology will be reported in detail elsewhere Direct and cross-tests by complement fixation with sera from lymphogranuloma patients and from Frei-negative trachoma patients, against the psittacosis-lymphogranuloma group antigen and against antigens prepared from strains TE8, TE55, and G1 revealed a very close relationship between all four antigens

Bacteriological Tests

Yolk-sac suspensions infected with both Chinese and Gambian strains of virus have been repeatedly seeded into various culture media, including those suitable for the growth of brucella and pleuropneumonia-like organisms Incubation under various conditions of temperature and atmosphere consistently failed to induce bacterial growth

Inoculation of Man

Discussing the criteria for identification of a cultured virus as the cause of trachoma the World Health Organisation (1956) stated

> "In all cases the final proof should be the production of typical trachoma in human volunteers after sufficient passages in culture to eliminate the dilution factor Although the committee deplores the necessity for human inoculation (not at present a dangerous procedure in view of effective chemotherapy) it insists that this criterion be fulfilled, as at the present time experimental trachoma cannot be diagnosed with certainty in hosts other than man"

It was deemed advisable to use a blind man for such an experiment, to avoid any possible risk to sight On March 11, 1958, such a volunteer was inoculated with strain-G1 virus from the 8th egg passage At this passage the original inoculum had been diluted about 10^{17} times

The blind volunteer was a white man, aged 71, whose right and left eyes were enucleated in 1955 and 1957 respectively after phaco-anaphylactic endophthalmitis Before inoculation the conjunctivæ of the sockets were not inflamed, though both were producing a slight mucopurulent discharge After the instillation of 4% cocaine drops the upper lids were everted, the tarsal conjunctiva and the fornix of the left eye were rubbed firmly with an eye swab soaked in a 20% suspension of infected yolk sac in broth-saline The right eye was similarly treated with a 20% suspension of normal yolk sac (day 0) The man was next seen on day 7 and was examined at intervals thereafter with a slit-lamp

Clinical observations—On day 7 he complained of soreness of his left socket, first noted on day 2 His right socket appeared unchanged and remained so thereafter except for slight hyperæmia (which appeared on day 17) of the lower-lid conjunctiva His left socket had a fairly profuse purulent discharge, and the entire conjunctiva was intensely congested, œdematous, and infiltrated His preauricular glands were neither palpable nor tender On day 10 he was not complaining, and his left socket was rather less congested On day 14 he had considerable papillary hyperplasia of the entire conjunctival surface of his left socket On day 17 there was increased discharge from his left socket, with increasing cellular infiltration On day 21 the conjunctiva of his left lower lid appeared granular, owing to small opaque foci, probably early follicles His left preauricular gland was just palpable and slightly tender On day 28 there was increased infiltration of the entire conjunctiva, otherwise there was no change since the last examination The left preauricular gland was no longer palpable or tender

Laboratory investigations—Cultures made on days 7, 17, and 21 yielded *Corynebacterium xerosis* from both sockets On day 17 two colonies of micrococci were grown from the left socket Examination of the volunteer's blood gave the following initial values Hb 16 6 g per 100 ml , packed cell volume 49%, white cells 9000 per c mm (polymorphs 63%, lymphocytes 33%, monocytes 4%), erythrocyte-sedimentation rate (Wintrobe) 10 mm in 1 hour These values remained substantially unchanged except for an increase in the proportion of polymorphs to 66% on day 14, and a rise in total white-cell count to 11,800 per c mm on day 21 Conjunctival scrapings were taken at each examination, and stained with iodine followed by Giemsa-May-Grunwald or by the latter stain only Scrapings from the right (control) conjunctiva contained only normal epithelial cells and moderate numbers of polymorphs From day 7 onwards scrapings from the left conjunctiva contained numerous polymorphs, on days 7 and 10 there were moderate numbers of lymphocytes, plasma cells, and large mononuclear cells The last three cell types became more numerous from day 14 onwards The epithelial cells often showed vacuolation of the cytoplasm, particularly near the nucleus, and distortion of nuclear structure On day 7 numerous particles were seen resembling elementary bodies, mostly extracellular but sometimes within the cytoplasm of the epithelial cells These bodies became progressively more scanty and were not seen after day 14 On day 7 a few initial bodies were seen in epithelial cells, and there were also very scanty but typical Halberstaedter-Prowazek bodies The presence of a carbohydrate matrix in the latter was proved by staining with iodine (Rice 1936, modified by Gilkes et al 1958), and the typical granular structure demonstrated by subsequent decolorising with alcohol and restaining with Giemsa-May-Grünwald (fig 2a and b) Initial body forms and Halberstaedter-Prowazek bodies (fig 3) became progressively more numerous until on day 21 there were often several visible in a single high-power field On day 14 material was inoculated into three chick embryos, one of which died with characteristic hæmorrhagic lesions 8 days later A yolk-sac smear showed numerous elementary bodies identical with those previously described

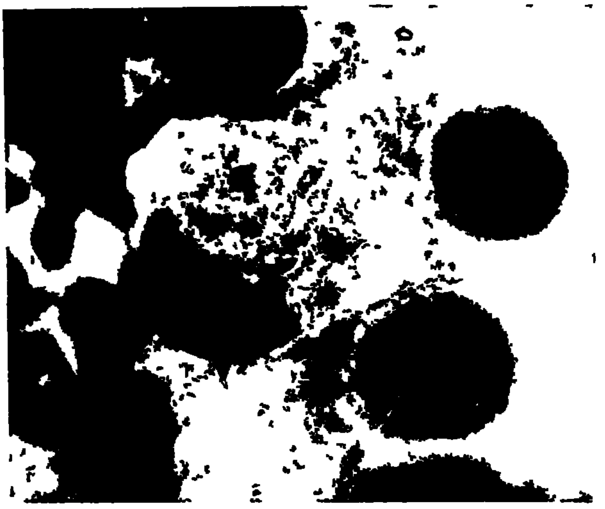
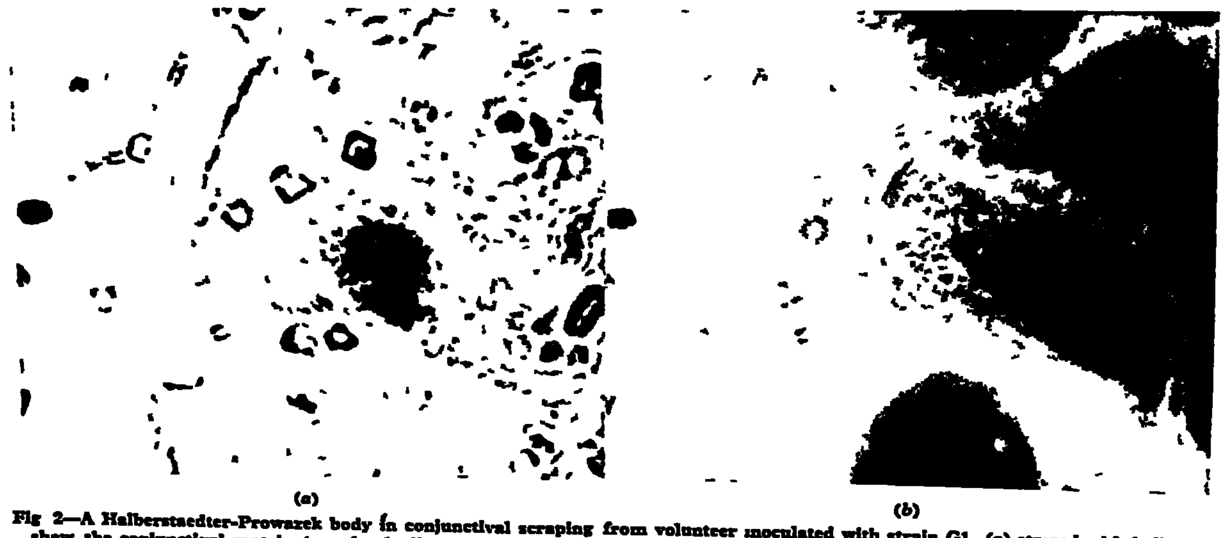


Fig 3—Conjunctival scraping from volunteer inoculated with strain G1 note epithelial cell containing large inclusion which fills cytoplasm and distorts nucleus (Giemsa-May-Grünwald ×1820)

Comment

Our experiments confirm the Chinese workers' findings that a virus resembling those of the psittacosis-lymphogranuloma group can be isolated from trachoma cases by yolk-sac inoculation Our electron microscopy and serological tests provide additional evidence of its



(a)

(b)

Fig 2—A Halberstaedter-Prowazek body in conjunctival scraping from volunteer inoculated with strain G1 (a) stained with iodine to show the conjunctival matrix (angular bodies are crystals of iodide), (b) decolorised and restained with Giemsa-May-Grünwald to show typical location and structure

estimation 2 (at the 5% level) No other statistically significant differences were found with any method of selection in any of the other tests, or in the patients' weights

Decreased platelet-stickiness, compatible with a decreased coagulability of the blood, together with a lowered serum-cholesterol, have therefore been demonstrated in a group of patients with ischæmic heart-disease after dietary restriction, compared with a group of patients with ischæmic heart-disease whose diet was not restricted

Discussion

The present investigation, which was made to determine the effect of a reduction of dietary fat on the coagulability of the blood in ischæmic heart-disease, has disclosed a significant reduction in platelet-stickiness under the conditions of the test Estimation of platelet-stickiness is one of four tests of blood coagulability which have previously been found to differ in patients with ischæmic heart-disease compared to controls, and to reflect hypercoagulability of the patients' blood (McDonald and Edgill 1957) In the remaining three tests (thromboplastin-generation, fibrinogen-estimation, and prothrombin-time) no significant difference was revealed after the diet It should not, however, be assumed, from this relatively brief period of dietary restriction, that blood coagulability as measured by these tests cannot be affected by the intake of fats and other substances in the diet

The difficulty of devising a really low-fat diet for ambulant outpatients is well known The rice-fruit diet was selected because it reduced the dietary fat and because other changes produced by it were fully described (Kempner 1948) The estimation of the 24-hour urine sodium provided independent evidence that the diet had been strictly maintained in an individual patient The serum-cholesterol may be reduced after the rice-fruit diet (Keys 1950), particularly where it has previously been high, a statistically significant reduction of serum-cholesterol was found in the patients studied A diet low in protein, as the rice-fruit diet is, may be accompanied by low serum-cholesterol Ahrens (1957), reviewing the subject, remained uncertain whether the low serum-cholesterol, with diets low in fat, might not be partly due to a low level of dietary protein The decrease in platelet-stickiness and the reduction of serum-cholesterol may be related, but many other humoral changes occur with the rice-fruit diet, a direct relation between these two is not yet proven Further investigation is being made to determine whether the decrease in platelet-stickiness is primarily concerned with changes in the blood-lipids, and, if so, whether it can be related to the dietary intake of any particular fatty compound

Two explanations seem possible for the continued reduction in platelet-stickiness 6–7 weeks after the end of the dietary period Firstly, the effect of the initial dietary restriction may have persisted, and secondly, although these patients were encouraged to resume a more normal diet, some only slightly modified their strict dietary regime, and particularly kept their fat-intake low Amongst Western people today there is a tendency for any patient with ischæmic heart-disease to restrict his intake of fat This factor, operating among the patients who acted as controls, would have tended to lessen the differences shown between those who had dieted and those who had not

The import of the difference in total platelet-counts found in the third method of comparison (low-sodium patients) remains at present uncertain; variation in total platelet counts has been noted at various stages in the natural history of ischæmic heart-disease (McDonald and Edgill unpublished), and seems to be related to platelet-stickiness

Although many patients on the diet claimed subjective improvement, no conclusive evidence was obtained that this regime had either significantly improved their symptoms or altered the course of their disease

Summary

Coagulability of the blood was studied in thirty-four patients with ischæmic heart-disease, before and after half of them had maintained a rice-fruit diet for 4–5 weeks

A statistically significant decrease in platelet-stickiness was found after the diet, together with a statistically significant decrease in serum-cholesterol and other changes No significant difference was found in thromboplastin generation, fibrinogen-estimation, and prothrombin-time (Russell's-viper venom, 'Stypven')

The cooperation and advice of Dr R G Macfarlane, F R S, and Dr Rosemary Biggs have been of the greatest value throughout this work, we express our thanks and indebtedness to them We thank Dr Paul Wood, director of the Institute of Cardiology, who has constantly supported this work, the physicians of the National Heart Hospital, who have allowed us to study their patients, Dr Helen Payling Wright, for advice on the platelet-stickiness test and for the loan of apparatus, Dr J O Irwin, who made the statistical analysis, Dr Denis Baron and Dr Reginald Hudson, for the serum-cholesterol estimations, Miss Wilkinson-Hughes, for help in preparation of the diet, Imperial Chemical Industries Ltd for a grant which covered part of the cost of the investigation, and Burroughs Wellcome and Co for a supply of 'Stypven'

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A MODIFIED VEIN-STRIPPER

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STRIPPING of the long saphenous vein is now fairly well established as the most useful single procedure in treatment of varicose veins In most cases, however tortuous the superficial veins may appear, the main saphenous trunk is straight enough to allow the stripper to be passed up its whole length from the ankle to the groin, and, if the stripping is complete, not only is the entire vein removed so that recanalisation is impossible but also most of the communications with the deep veins are torn across The superficial varicose tributaries are also disrupted at their junction with the main vein and, since most of them are fed from above by this source, they thrombose or collapse and cause no further symptoms

In about 90% of cases this treatment is sufficient to relieve all symptoms and gives an excellent cosmetic result—an important consideration in a disease many of whose victims are young women Patients requiring further treatment fall into two groups

(1) Those with persistent superficial varicose tributaries, which may be removed by small tenotomy-sized incisions through which they may be fished out with the blunt end of a curved needle

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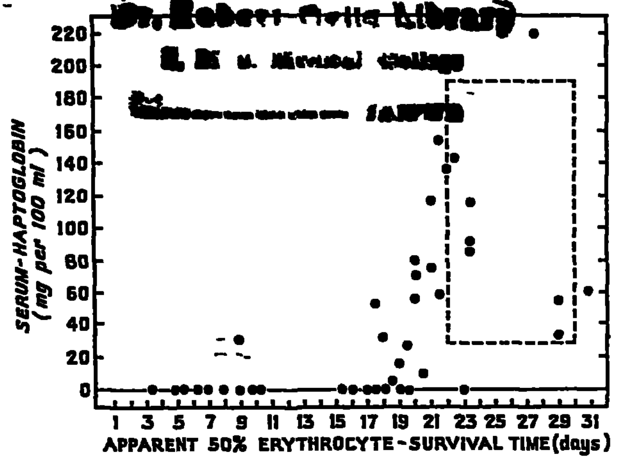

Relationship between serum-haptoglobin level and apparent 50% erythrocyte-survival time (40 determinations in 36 patients with either anæmia or indirect hyperbilirubinæmia) Broken line encloses normal range

The haptoglobin level was determined by the method of Jayle[7] (normal value 109 mg per 100 ml, 95% range 28–190 mg per 100 ml) The erythrocyte-survival time was determined after tagging the erythrocytes with ^{51}Cr in vitro The activity of blood drawn 10 minutes after the injection was taken as 100% (normal 50% apparent survival time 26 days, range 22–30 days) The serum-methæmalbumin level was determined electrophoretically[8]

The results are summarised in the accompanying figure When the survival time was normal, the haptoglobin level was not depressed, whereas patients with 50% apparent survival time of less than 17½ days proved to have ahaptoglobinæmia—i e, no measurable amount of haptoglobin in the serum In the intermediate group with a 50% survival time of 17½–22 days the serum-haptoglobin level was normal or depressed, tending to vary with the survival time

There were two exceptions to these rules, but in these cases the clinical picture was also somewhat unusual

Case 1 had a very short survival time (apparent 50% survival time 9 days), but the haptoglobin level was regularly about 30 mg per 100 ml This patient also had erythropoietic hyperplasia of the bone-marrow, hyperbilirubinæmia, and increased excretion of bile pigments—all signs of increased erythrocyte turnover In spite of this the number of reticulocytes was not increased, nor was there any evidence of active disease (normal erythrocyte-sedimentation rate and normal electrophoretic pattern of serum-proteins)

Case 2 had ahaptoglobinæmia despite a normal survival time of the circulating erythrocytes In this case, too, there was an increased excretion of bile pigments, but the reticulocyte count was normal despite erythropoietic hyperplasia of the bone-marrow This patient appeared to have bone-marrow dysfunction ("bone-marrow hæmolysis") with increased production but low release of erythrocytes

Depression of the haptoglobin level must be due either to decreased production or to increased elimination of haptoglobin Hæmoglobin injected intravenously forms a complex with haptoglobin, which is readily eliminated from the blood-stream After all the haptoglobin has been eliminated in this way, the normal level does not return until after several days

These observations[8] may explain ahaptoglobinæmia in diseases with associated intravascular release of hæmoglobin Judging from the appearance of methæmalbumin in the serum, only 2 of our patients had intravascular hæmolysis, and both had ahaptoglobinæmia Though no certain explanation can be offered for the depression of the serum-haptoglobin level in the other cases, it seems reasonable to assume an increased consumption due to the increased turnover of hæmoglobin

Ahaptoglobinæmia is rare in diseases other than hæmolytic and pernicious anæmia It has been found in hepatocellular failure[2 9] (in which the destruction of the red blood-cells may, however, be increased[10]) and in a few exceptional cases without anæmia[9] Hormone therapy also can influence the haptoglobin level[9 11]

Our preliminary results show that determination of the haptoglobin level is useful in the investigation of anæmia A normal or a raised level argues strongly against hæmolysis, whereas a low level in the absence of hepatic disease indicates hæmolysis Determination of the haptoglobin level is both simple and quick, and it is possible, by repeated determinations, to follow the course of a disease even in patients not in hæmatological equilibrium, in whom the erythrocyte life-span is difficult to assess

The investigation was supported by grants from the Swedish Medical Research Council to B F N and from the Medical Faculty of the University of Lund to M N

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Medical Societies

BRITISH ASSOCIATION OF PHYSICAL MEDICINE

The annual meeting was held in London on April 25 and 26 under the presidency of Dr P Bauwens

Systemic Manifestations of Rheumatoid Arthritis and Pararheumatic Diseases

Dr A T **Richardson** (London) said that in collagen diseases changes in the serum-globulins were an important factor, but the chemical, physical, and serological reactions in everyday use indicated fundamental differences between these diseases With modern diagnostic techniques such as biopsy, serological tests, and electromyography a firm diagnosis could usually be made But clinical advances were likelier to be mad if the collagen disorders were regarded as separate entities

Dr R M **Mason** and Dr V L **Steinberg** (London) h observed 15 cases of rheumatoid arthritis with [illegible] complications In 6 there was pleural effusion, and [illegible] these the onset of the effusion was closely related to a [illegible] of joint activity Of 9 cases exhibiting diffuse parenchy lung changes, pneumoconiosis or lipoidosis was shown the cause in 4, 1 case was found to be systemic lupus ery matosus (S L E), and the remaining 4, in which no cause cou be found, might be presumed to have "rheumatoid lung" Dr Mason had observed 5 cases of peripheral neuropathy complicating rheumatoid arthritis and 1 case of peripheral neuropathy complicating probable S L E Neuropathy, which appeared to indicate a bad prognosis, was commonly sensory (though motor changes might follow) and usually presented with paræsthesiæ and numbness, generally of the lower limbs Arteritis in association with rheumatoid arthritis had been recognised only quite lately, it was thought to be an infrequen but serious complication It seemed reasonable to conclud that in addition to the frank arteritis of superficial tissues oth complications of rheumatoid arthritis, such as peripheral neur pathy and possibly pleural involvement, might be manifest tions of arteritis It was not clear whether this complic was associated directly with steroid therapy or merely with

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[7] Jayle, M F *Bull Soc Chim biol* [illegible]

[8] Laurell, C B., Nyman, M *Blood*, 1957, [illegible]

[9] Nyman M, unpublished

[10] [illegible] J H *J clin Invest* 1955, 34, 390

[11] von Studnitz, W, Nyman, M *J clin Endocrin* 1957, 17, 910

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severe type of rheumatoid disease that was likely to be treated by steroids, but it seemed that sudden withdrawal of these drugs might set off diffuse necrotising arteritis

Dr A C **Boyle** (London) said that S L E was the commonest of the pararheumatic diseases presenting in departments of physical medicine, by virtue of the frequency of myalgia, arthralgia, or arthritis as the predominant feature This disorder should always be suspected where the symptoms in the joints were out of proportion to objective signs of joint involvement, or where radiographs showed less destructive change than the clinical picture would suggest To the dermatologist S L E presented as a skin disease with involvement of the viscera and sometimes the joints, to the general physician it presented as a general illness, while to the physician in physical medicine it presented as a disease of the joints with involvement of the viscera and sometimes the skin The discovery of the L E-cell phenomenon had made possible the detection of a hitherto unsuspected group of cases which appeared to be low grade and which carried a relatively good prognosis The L E-cell phenomenon was an empirical test, but, in some cases where a diagnosis of S L E was strongly suspected on clinical grounds and yet the test remained negative, a positive result might be obtained by giving the patient 30–40 units of corticotrophin for two to three days and then repeating the test Dr Boyle believed that the L E-cell test was specific for S L E, and a positive result in a case of apparently uncomplicated rheumatoid arthritis heralded systemic involvement The diagnosis of S L E should rest on the clinical features and not on an isolated pathological finding, but conversely a negative L E-cell test did not exclude this diagnosis

Dr S **Mattingly** (London) reviewed clinical and pathological features of some of the rarer collagen disorders In polyarteritis the abdominal manifestations were commonly misinterpreted as an abdominal emergency requiring laparotomy, in the acute stage an acute infection might be simulated Dermatomyositis was associated in about 20% of cases with a malignant tumour Thrombotic thrombocytopenic purpura, a rare condition that was supposedly a "collagen disease" and was thought to comprise a generalised vascular disorder affecting the intima of all small blood-vessels, it might possibly be associated with allergy to drugs and microorganisms The rarer collagen diseases should be considered in the differential diagnosis of obscure joint or muscle pain, particularly when associated with skin lesions, fever, hypertension, or renal disease

Mucoprotein Levels in Rheumatoid Arthritis

Dr C **Feldman**, Dr E V **Hess**, and Mr R L **Markham** had made a long-term assessment of 23 patients with rheumatoid arthritis, including estimation of the two mucoprotein levels, M1 and M2, by photometric scanning following staining of the polysaccharide moiety of the electrophoretically separated fractions, the levels were expressed in arbitrary figures In normal controls the range for M1 was 5–22 units, and for M2 10–26 units In the patients M1 ranged up to 90 units and M2 up to 250 units The range of mucoprotein values was similar in the different stages of disease, except that high values were absent in Steinbrocker's stage I, and the mean values were not significantly different The mean values were much higher in the moderate than in the slight cases, but in the severe cases the values were no higher than in the moderate cases In 6 patients with inactive or slight disease activity M1 showed normal values over a period of at least two months, while the *M2* values remained raised, and in 7 patients with moderate or severe disease activity M1 (but not *M2*) values returned to normal on single occasions This suggested that levels of *M2* more closely reflected the severity of the disease There were wide fluctuations in mucoprotein levels between consecutive readings in individual patients, although the overall pattern correlated satisfactorily with clinical assessment A cautious approach was needed in assessing results of single readings, but serial readings were probably a more reliable aid to clinical assessment than the erythrocyte-sedimentation rate (E S R) or C-reactive protein test

Laboratory Indices in Rheumatic Disease

Dr J H **Glyn** (London) said that it was becoming increasingly clear that the E S R was a fallible guide in screening sorting patients who attended departments of p medicine complaining of ill-defined symptoms In 330 pa with various rheumatic disorders there had been a st correlation between clinical activity and the following te C-reactive protein, total protein-bound polysaccharides, protein, and protein polysaccharides ratio In estab disease these gave fewer false negative readings than the Unfortunately all the tests had been found disappoin unreliable in diagnostic dilemmas, and there was no justi tion for recommending the routine performance of such ti consuming procedures

Therapeutic Trials in Lumbar-disc Degeneration

Dr J **Stewart Lawrence** (Manchester) reported an inve gation into the treatment of miners with pain of lumbar sciatic distribution associated with radiographic evidence disc degeneration but with no neurological signs Immob tion of the lumbar spine by either a plaster ct or bed was found to delay recovery Mobilisation, he other h produced a significantly better result, and manipulation by physiotherapist was more effective than ionisation Acti mobilisation of the spine by exercises was still more effecti Massage produced temporary relief of pain, although appeared to have no influence on the outcome of the mala and did nothing to hasten return to work Cortisone given by mouth to patients in the acute stage of their disability produc no significant difference judging by comparison with simila cases treated by a suspension of cholesterol The value of light spinal support to heavy manual workers as a preventi to future painful and disabling attacks of pain remained unproven

Injuries to the Collateral Ligaments of the Knee Joint

Flight Lieutenant V B **Whittaker** described the results in 83 cases of injury to the collateral ligament No case with associated meniscus or bone injury was included The rati of medial to lateral ligament injuries in this series was 7 1, and, as in meniscus injuries, association football was responsible for the large majority of cases Treatment by complete immobilisa tion, with or without operative repair, produced successful results in a higher proportion of cases (89%) than treatment by other less radical methods, such as heat therapy, strapping manipulation, rest in back splint, or no treatment at all with each of which the success-rate was (50%) Immobilisa tion in plaster-of-paris for five to six weeks was necessary to achieve a good result In the 2 failures recorded in this series of 83 cases immobilisation had been maintained for less than three weeks

OPHTHALMOLOGICAL SOCIETY OF THE UNITED KINGDOM

The annual congress was held in Cardiff on April 17–19, under the presidency of Mr J J **Healy**

Complications and Treatment of Hypermature Cataract

Mr G T W **Cashell** (Reading) said that of the complica tions of hypermature cataract secondary glaucoma and uveitis were the most important An anterior hypermature lens might prevent glaucoma

Mr C A **Cook** (London) considered the pathological aspects of these complications, which he described under two main headings (1) those leading primarily to the production of glaucoma, and (2) conditions in which the primary pathological change is inflammatory and which may or may not be responsible eventually for a secondary increase in intra ocular pressure Included under (1) were phacolytic glaucoma, the hypermature intumescent lens, and the hypermature dis located lens; and under (2) the so-called lens-induced uveitis, was subdivided into phacotoxic uveitis and endophthal- haco-anaphylactica

J R Hudson observed that the hypermature cataract s common than in the past, and its complications were encountered The early signs of hypermaturity should, absence of any general contraindication, be taken as an ion for operative treatment of a cataract

Fanconi's Syndrome

S J H Miller (London) described a case of Fanconi's ome with pseudofractures which had been treated with rol The calcium deposits that had developed within the were dispersed by maintaining the patient in mild is

Carbonic-anhydrase Inhibitor

M E Langham (London) reported his observations on fect of 'Neptazane' on the intraocular pressure of rabbits nan Neptazane, a new inhibitor of carbonic anhydrase, ed into th[illegible] more readily, while leaving the body more y, than acetazolamide ('Diamox') When neptazane given intravenously both the intraocular pressure and the of formation of the aqueous decreased rapidly

Toxoplasma in Ocular Disease

of C P Beattie (Sheffield) said that toxoplasma had a larly wide zoological and geographical distribution, with revalence of infection in man varying from 5% in Iceland % in Tahiti In this country about a quarter to a half of dult population had been infected In the congenital form, e at least the placental route of transmission was definite, oretinitis was the most constant manifestation, and indeed toxoplasmic chorioretinitis was congenital The acquired tions were usually innocuous, causing only a lymphadeno- y that resembled glandular fever

J K A Beverley (Sheffield) described evidence that in highly immune animals the organism could multiply

r E S Perkins (London) emphasised that there is now statistical, therapeutic, and pathological evidence that plasmosis may cause uveitis in adults as well as a congenital ioretinitis Unfortunately, serological evidence of infec- with toxoplasmosis was common in healthy adults and, e a negative dye test probably excluded toxoplasmosis, a tive test did not prove the ætiology of an individual case of itis Possibly some cases of anterior uveitis were due to plasmosis, but at the moment these cases could not be gnised clinically A positive dye test was common in terior uveitis—particularly acute and subacute cases Cases veitis with a positive dye test were characterised by focal ches of chorioretinitis near the main retinal vessels or the cula or at the margin of the optic disc In many cases the ve lesion was at the edge of an old scar, suggesting that the ority of these lesions were recurrences of congenital infec- s Disseminated choroiditis was not associated with a itive dye test, and was unlikely to be due to toxoplasmosis, the results in retinal vasculitis suggested that toxo- smosis was not a common cause of this condition

Precancerous Melanosis of the Conjunctiva

r M Lederman (London) assessed his results in 14 cases cancerous melanosis at the Royal Marsden Hospital, ndon Of those 14, 12 were submitted to radiotherapy Of se, 2 died of metastases, and the remainder had survived up to seven years, so at any rate some of these tumours re radiosensitive Beta-radiation was to be recommended ause of the relative lack of complications

Chronic Uveitis

Mr A G Cross (London) said that the treatment of chronic itis has been revolutionised by the introduction of the enocortical hormones, which readily damped down the te cases till they had run their usual short and predetermined rse But the outlook, although much better than ten years , was still often grave, blindness resulting

Tolazoline Test

Mr J A E Primrose (London) described the tolazoline ('Priscol') test in glaucoma This test produced a small but transient increase in tension in normal eyes, but in 50 cases of chronic simple glaucoma there was a mean rise in tension of 12 2 mm Hg, while in most cases of narrow-angle glaucoma the response was normal The tolazoline effect was probably due to its influence on the vessels because of an increased formation of aqueous humour

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Reviews of Books

An Introduction to Experimental Surgical Studies

W J Dempster, F R C S, lecturer in experimental surgery, Postgraduate Medical School of London Oxford Blackwell Scientific Publications 1958 Pp 463 50s

The surgeon today stands like Cortez upon a peak, rubbing his eyes at the new vistas offered to him by the rapid developments in science Yet he must have regrets that many of these visions may be denied to him as realities because of his own limitations By separating the basic sciences so completely from clinical vocation the medical curriculum has in the past effectively sterilised what scientific education most surgeons received, and has conspired with the exigencies of his craft during its anatomical era to rob him of scientific understanding and know-how Yet a new scientific age for surgery has begun and must be carried forward by men who cannot be regarded as professionals in the scientific sense, until a new generation with a different outlook displaces them

The importance of Mr Dempster's work lies in the tacit acceptance of this situation It would, of course, be a herculean task at this stage to develop a book on the application of the basic sciences to surgery, Mr Dempster starts one stage further by providing the surgeon with means of informing himself at the physiological level of experimental empiricism The implication of the word "introduction" in the title should not be misconstrued, for this is not a work for the tyro to read overnight on seeking appointment to a professorial unit It is introductory in the sense that the man tackling a specific problem can find not only an account of the basic work already undertaken in that field but also a useful bibliography, it is crammed with facts and is not armchair reading

To some it may seem that the author's approach has been limited, since he has confined himself to the problems of healing, grafting, transplantation, and low temperature in general, and in particular to the thoracic, genitourinary, gastro-enterological, and cardiovascular aspects But this would be carping criticism, for here is something new arising from an original and courageous conception and completed only with considerable labour Such a book will need frequent new editions since it is valueless if it does not keep up to date, its relatively low price is therefore important Mr Dempster is to be congratulated for his idea, his labour, and the service he has performed

Cancer

Editor Ronald W Raven, F R C S, surgeon, Royal Marsden Hospital, London London Butterworth 1957 Vol 1, pp 557 Vol 2, pp 666 85s each

To produce a System of Cancer is a formidable task at this time of expanding knowledge, and although this work comprises 6 large volumes and an index volume, the specialist must naturally expect to find gaps in the parts which cover his own special interest this could not be otherwise if the work was to be a reasonable size

The first two volumes, which have just appeared, are concerned with research into causation and with the pathology of human tumours Succeeding volumes are to cover epidemiology, occupational cancer, cancer education and detection, clinical aspects, and radiotherapy and chemotherapy The editor contributes several clinical chapters, but the general aim has been to enlist the help of many authors of differing tastes and knowledge to write chapters on their own specialty

To relieve cardiac œdema or pulmonary congestion, it is necessary to reduce the sodium content of the body, an increased excretion of water alone, or of an anion unaccompanied by sodium, is in this context irrelevant In theory the ideal diuretic would increase the amount of sodium filtered by the glomeruli, or diminish directly the amount of sodium reabsorbed by the tubules, in practice the most effective agents at present are those which act primarily by diminishing chloride reabsorption, the increased output of chloride being then accompanied by natriuresis When the general treatment of a cardiac invalid with rest and digitalis is effective, the glomerular filtration-rate (G F R) increases and œdema may be prevented or diminished, so comparatively ineffective diuretic agents may appear to have worked efficiently The diuretic action of theophylline drugs depends mainly on an increase in G F R, and some patients who have become resistant to mercurials may respond once again when aminophylline in a dose of up to 0 5 g is given intravenously two hours after the mercurial injection[6] VOGL[7] advocates the use of oral theophylline preparations as an adjuvant to diuretic therapy Decreased reabsorption of sodium can be directly effected by inducing an osmotic diuresis or by inhibiting the production of aldosterone, which is often increased in œdematous patients[8] Interest in urea as an oral osmotic diuretic has recently been revived[9], but large doses are needed, and the incidence of anorexia and nausea is fairly high The production of aldosterone can be inhibited by amphenone,[10] but the toxic effects of this drug preclude its therapeutic use

Several drugs act mainly by depressing anion reabsorption The carbonic anhydrase inhibitors, which depress bicarbonate reabsorption, are of little value in the treatment of œdema, for they quickly lose their effect as the plasma-bicarbonate level falls, and with it the amount of bicarbonate filtered into the nephron, there is also a tendency to a greater loss of potassium than with mercurial diuretics[6] Since the amount of chloride entering the nephron is normally about three times as great as the amount of bicarbonate,[6] there is a greater potentiality of effectiveness for drugs which depress the reabsorption of chloride rather than of bicarbonate Three groups of drugs have been tested fairly extensively as oral chloruretic agents These are the oral organic mercurials, the aminouracil compounds, and substituted benzothiodiazine (chlorothiazide)

Oral mercurials, such as chlormerodrin ('Merchloran'), may cause diarrhœa, whether because they inhibit fluid absorption in the bowel as well as in the nephron or because the intestinal epithelium is highly susceptible to mercurial toxicity, and we agree with the view of GOODMAN and GILMAN[11]

> "The oral administration of mercurial diuretics obviates the necessity of injection at the price of gastro-intestinal irritation, higher total dosage of mercury, greater danger of systemic mercury poisoning, and a more delayed and less complete diuretic response The route is ineffective when a rapid mobilisation of œdema fluid is desired in an acutely ill individual"

Their final comment applies, we believe, with equal force to the aminouracil compounds While these have some diuretic potency, the incidence of side-effects is high, especially with aminometradine ('Mictine'), the frequency of side-effects is distinctly lower with amisometradine ('Rolicton'), and this drug was found to be of some value in preventing recurrence of œdema which had been got rid of by mercurials[12] The aminouracil compounds quickly lose their effect, and do not really stand comparison with organic mercurials[13] Chlorothiazide is in a quite different category of effectiveness from the oral mercurials and the aminouracil drugs

In potency it is comparable to the mercurials given by injection, and may even produce diuresis in patients who have become resistant to mercurial diuretics[14 15] Favourable clinical reports on its effectiveness in generalised œdema have appeared both in America[14 16 17] and in this country[14 18] It does seem that we now have a potent oral diuretic that not only can control œdema but also, for good measure, has some hypotensive action[19] If our satisfaction at this should appear a little half-hearted, it is because we foresee possible abuse of a drug which, though convenient and potent, is also expensive and not devoid of side-effects Gastrointestinal side-effects seem to be uncommon, but potassium depletion has been observed[14 15], this can be controlled by giving daily supplements of 2–6 g of potassium chloride[15] One patient had an erythematous rash which disappeared when the drug was stopped[17] Hypochloræmia has been observed in patients taking chlorothiazide,[13] but should be controllable by ammonium or potassium chloride The cost is also of some importance According to a pricing bureau the basic cost to the N H S of three injections of mersalyl is 1s 5d, whereas the basic cost of 8 g of chlorothiazide is 9s 10½d, the cost of a week's treatment of œdema is thus more than six times as great with present oral treatment No doubt the need to give injections carries substantial overheads above the basic cost, but at least the diuretic has been given, and there is no box of tablets to constitute a problem of domestic pharmacognosy or of self-medication in the next minor illness

Chlorothiazide certainly represents a great advance in diuretic treatment May we hope that it will become cheaper, that it will not replace the well-tried mercurials until we know more of its side-effects, and, above all, that it will not be used to treat every patient with hypertension, or who complains of breathlessness or swelling of the ankles

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Tetanus

TETANUS has been recognised as a killer since its lescription by HIPPOCRATES. By reason of the mode of nfection, the distressing signs, and the difficulty of reatment, it is a dramatic disease. The extent of its menace varies widely from one country to another. Among European countries, it kills each year 22 per million in France, Spain, and Yugoslavia, compared with only 1.7 per million in Great Britain.[1] In agricultural communities the incidence is, of course, higher, and in Brazil in the first quarter of the century the mortality was 178 per million. The efficacy of preventive inoculation is beyond question. In the first six months of the 1914–18 war there were 17,800 cases of tetanus among half a million wounded. Between 1942 and 1945 there were only 12 cases of tetanus in the United States Army,[2] in which preventive inoculation was the rule. Part of this reduction was doubtless due to the absence of horses in the latter period, but the contrast is nevertheless impressive.

Tetanus is not yet so rare as to be unimportant, but in Great Britain it *is* so rare that few people or groups can number more than a handful of cases in their experience. This makes it difficult to evaluate any new treatment, and important to draw as many conclusions as possible from collective experience. The three papers appearing in our present issue and the previous one should be considered in conjunction with last year's report from the Charity Hospital, New Orleans.[3] In the previous fourteen years as many as 558 cases were treated at this hospital. The span of fourteen years was divided into two equal periods, in the second of which antibiotics, tracheostomy, muscle relaxants, and gastrostomy were adopted. This provided as good an opportunity as any that is likely to arise to establish the value of these newer forms of treatment. The mortality was 10% lower in the second period than in the first. But even this modest reduction is robbed of much of its significance by the fact that there has been a steady decrease in mortality during the past fifty years, and the New Orleans workers hold that general supportive care is more important than any single component of treatment.

Of the newer forms of therapy, the muscle relaxants seem to offer great possibilities, and those who have faced the difficulties of their continued use for days or weeks and at last seen the patient go home cured (as did Dr WILTON and his colleagues, whose paper appeared last week) would be unwilling to agree that this is an unimportant advance. The idea behind it—of converting a spastic patient whose respiratory mechanism is out of control into a flaccid patient whose respiration will accept control—has an appeal which is strengthened by the success of the modern treatment of respiratory paralysis. The slightness of the apparent effect of the relaxants on the mortality in the American series may be attributable to insufficient dosages, for they were not used at the Charity Hospital in the manner recommended by their advocates in this country.

Another drug which may have an important place in the treatment of tetanus is chlorpromazine, which is the subject of the papers this week by Dr LAURENCE and his colleagues and by Dr BARR, and its use has been reported by many other workers, including those from the Charity Hospital. Undoubtedly chlorpromazine can dramatically reduce spasticity, sometimes without greatly clouding consciousness or causing significant respiratory depression. LAURENCE et al. describe a valid comparison between chlorpromazine and the barbiturates. In this trial chlorpromazine did not appear to save more lives than the barbiturates, though its administration was easier to manage.

Despite a wealth of reports, we are still in doubt about the best method of treating this challenging disease. For instance, we still have no clear evidence whether hypertonia is better offset by muscle relaxants or central depressants. On the other hand, in the past five or six years we have learnt a good deal about the management of respiratory inadequacy. As it is this that usually kills the patient who succumbs to tetanus we might feel optimistic, but those with experience in treating the disease know only too well how commonly, despite all precautions, an unexpected asphyxial crisis carries the patient off. Even if we could always avoid asphyxia and invasion of the lungs, some patients with severe tetanus might inevitably succumb instead to fixed neurotoxin, which many believe to be unassailable by antitoxin.[4] A short incubation period and a rapid march of symptoms denote a bad prognosis, but not a hopeless one; several very severely afflicted patients have been saved by careful treatment. Clinicians differ in their choice of drugs, but protection of the lungs from invasion, the annulment of hypertonia, the maintenance of adequate respiratory exchange, and tireless supportive care clearly remain the foundations on which treatment should be based.

Annotations

THE OUTPATIENT DEPARTMENT

THE proper function of the outpatient department has hitherto not been given sufficient thought. A discussion by the hospital section of the Royal Society of Health at its congress in Eastbourne last week was therefore most opportune. In this discussion Dr John Fry pointed out that there has been a tendency to over-stress the role of the hospital in providing inpatient care and to neglect the work of the outpatient department, whereas in terms of service to the public the outpatient department is far more important. He suggested that there is an urgent need to look into the present functions and work of the outpatient department and to plan for the future.

Dr A. G. Emslie thought that patients usually much prefer, instead of being admitted to hospital, to attend as outpatients, for this disturbs their home life less. Owing to great advances in radiological and pathological techniques and in therapy, many more patients than formerly can now be investigated and treated as outpatients. It was agreed that this trend should be encouraged, and the functions of the outpatient department will clearly have to be reconsidered Dr Fry sees the outpatient departments filling three main roles—that of consultation centre, that of diagnostic centre, and that of supplying special investigations and treatment

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[1] Anders, W. *Aerztl. Wschr.* 1952, 7, 1112.

[2] Lond, A. P., Sartwell, E. P. *Bull. U.S. Army med. Dep.* 1947, 7, 371.

[3] Creech, O., Glover, A., Ochsner, A. *Ann. Surg.* 1957, 146, 369.

[4] Ransom, F. *Lancet*, 1917, ii, 928.

Dr Emslie emphasised that outpatient work should include radiological and pathological investigations, and the almoner service is another important element Dr Fry pointed out there is considerable variation between general practitioners in the number of patients they refer to consultants Do these differences depend, he asked, on individual factors such as the doctor's age, his education, the size of his list, or his family responsibilities? The discussion showed that we really need to know more of the medical, social, and other factors that may influence referral The average family doctor refers to the consultant in hospital only some 10% of his cases, but where radiological and pathological facilities are afforded to general practitioners these facilities are extensively used Fry himself, out of about 5000 patients at risk in any one year, refers 450 to a consultant, either as outpatients or as inpatients, and a further 320 directly to the radiological department and 375 to the pathological department

There is no doubt that the use of outpatient departments will increase in the future, and it seems sensible to foster this increase by devoting capital money to the construction or extension of these departments Allowance will have to be made for further special facilities—including provision for electrocardiographic examinations and investigations with radioactive isotopes In time the outpatient department may establish itself as the main link not only between the general practitioner and the hospital but also between the preventive services, directed by the medical officer of health, and the hospital Those participating in the discussion agreed that outpatient facilities should be associated with existing hospitals, and some doubt was expressed as to the value of "peripheral clinics" for diagnosis and consultation There is much scope for research in the design of outpatient departments—including if possible the provision of outpatient beds in addition to casualty-recovery beds where patients can be retained for six to eight hours for observation or for minor surgical or medical procedures

POSTOPERATIVE PAROTITIS

PAROTITIS not due to mumps was recognised as a complication of febrile illness, notably typhus, by Stephen Paget[1] He recorded that parotitis, sometimes with suppuration, might follow diseases in the abdomen or pelvis without any signs of pyæmia or septicæmia Paget and some of his contemporaries believed that this complication arose because of some complex connection between the parotid gland and the peritoneum and generative organs—a development of the observation by Hippocrates that orchitis was a complication of mumps

Parotitis sometimes follows operation The exact pathogenesis is uncertain, but the infection, which is usually staphylococcal, probably reaches the gland by way of the parotid duct Dryness of the mouth resulting from a poor flow of saliva and lack of attention to oral hygiene are recognised predisposing factors In 1955 Robinson[2] concluded, from a survey of hospital records, that parotitis had practically disappeared as a postoperative complication He observed that the incidence of this complication did not decline until the advent of antibiotics, though the mortality from it fell after the introduction, about 1930, of radiotherapy as a remedy Robinson held that the free use of antibiotics after operation probably accounted for its almost complete disappearance, and that better control of fluid and electrolyte balance and improved oral hygiene were minor factors He argued in favour of antibiotic prophylaxis, but foresaw the potential danger of this practice in a warning that antibiotic-resistant staphylococci might, in the future, give rise to a rebirth of the condition, and now Brown et al[3] have reported a twelvefold increase in the incidence of postoperative parotitis at the U S Naval Hospital, San Diego, California

The incidence rose from 2 in 171,826 operations in 1949–56 to 7 in 47,947 operations in 1956–57 Of the 7 affected patients 3 died, and parotitis was twice held partly responsible for death This serious complication was commoner in patients who had a stormy postoperative course, but it could be the only incident in an otherwise uneventful convalescence *Staphylococcus aureus* was isolated from the parotid gland in 5 of the 7 cases, in the other 2 patients the lesions were aborted by early treatment Unfortunately the antibiotic-sensitivity pattern of the staphylococci was not recorded Brown et al believe that this complication is likely to be related to the increasing number of carriers of antibiotic-resistant staphylococci in every hospital community In fact, however, they report that only 7 of 136 cultures of nasopharyngeal secretions from hospital workers yielded *Staph aureus*—a carriage-rate of only 5% (This is an astonishingly low figure, the rate is usually about 50%) But nasal carriage is by no means the only important factor in the spread of staphylococci in hospitals[4]

We have deplored the abuse of antibiotics in prophylaxis[5], and these substances have no part to play in the prevention of surgical parotitis It can only be hoped that this dangerous complication may be avoided by common sense attention to fluid balance and oral hygiene, and by energetic measures to restrict the spread of hospital staphylococci[4–6] Staphylococcal parotitis, once established, can progress so quickly that early diagnosis and treatment are essential An antibiotic to which the hospital staphylococcus will probably be sensitive—chloramphenicol, erythromycin, or novobiocin—should be administered, and, in the experience of Brown et al early radiotherapy is still of value If these measures fail to limit the infection, surgical drainage should be established without delay It remains to be seen whether parotitis is to become yet another manifestation of the staphylococcus plague[7]

RETINAL PHOTOGRAPHY

SKILLED ophthalmoscopy yields information not only about local conditions but also about general disorders But the technique is not easily mastered, and even an experienced ophthalmoscopist finds difficulty in describing his observations A short period in an ophthalmic department is enough to impress beginners with the differences between reports on a single fundus by a group of experts, and serial observations of a progressive fundus lesion, made in ignorance of previous records, show how open to error the method is Many progressive retinopathies, such as those associated with hypertension, diabetes, and suspected intracranial tumours, demand more accurate observation than is possible with ophthalmoscopy, and ophthalmologists are therefore turning to photography for objective records

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[1] Paget, S *Lancet*, 1886, i, 732

[2] Robinson, J R *Surgery*, 1955, 38, 703

[3] Brown, J V, Sedwitz, J L, Hanner, J M *U S Armed Forces med J* 1958, 9, 161

[4] *Lancet*, March 8, 1958 p 515

[5] *ibid* Jan 4 1958, p 37

[6] *ibid* Feb 8, 1958, p 301

[7] *ibid* 1957, i, 723

The Zeiss-Nordenson retinal camera, introduced in 1915, depended for its light source initially on a carbon arc and later on a filament lamp

> An image of this source was formed by optical means at the margin of the dilated pupil and a cone of light entered the eye and illuminated an area of the retina An aerial image of the illuminated fundus was formed within the instrument by a powerful convex lens as in indirect ophthalmoscopy, and this aerial image was photographed by a built-in camera designed on the principles of a single-lens reflex camera

The Zeiss-Nordenson camera gave good monochromatic photographs of the retina with exposures of a tenth to a twenty-fifth of a second, but such long exposures were liable to cause failures due to blinking and ocular movements, and with colour photography (calling for exposures of a half to a fifth of a second) failures were even commoner Modern developments in lighting have led to successful colour photography with fast exposures[1-4] For this purpose a high-speed electronic discharge flash-lamp has been incorporated in the Zeiss-Nordenson camera, or this camera has been adapted to a xenon-arc lamp But there is a great demand for entirely new models, and Hansell[5] describes seven which have appeared in the last year or so Most are based on the Gullstrand ophthalmoscope and Zeiss-Nordenson camera

> Illumination for focusing is usually independent of that for photography In most, colour photographs can be taken by rapid exposure with an electronic flash One camera compensates not only for refractive errors including astigmatism but also for chromatic aberration in the human eye 35 mm film is standard, and most models have standard detachable camera bodies which may be interchanged with other instruments

Despite all this effort, retinal photographs, even in colour, leave much to be desired, and it remains more difficult to recognise a retinal condition from a photograph than from an artist's painting Admittedly this may be partly because the artist, like the ophthalmologist, has preconceived notions which bias his observations, but the artist can give a satisfying Mercator-like projection of the fundus which resembles the subjective impression on examining the retina It is difficult to imagine an optical device which could do this—or a suitable method of illumination In this respect modern retinal cameras are less satisfactory than the original Zeiss-Nordenson camera, for with them the photograph records a smaller area of fundus, and consequently a clinician who needs a record of, say, the whole length of a retinal blood-vessel, must take serial photographs and piece them together Some of Leishman's[6] excellent illustrations are composed of eleven separate photographs A further difficulty for the clinician wishing to use the retinal camera as a research tool concerns magnification The size of the retinal details depends not on refractive error but on the total refractive power of the eye For example, the optic disc will be smaller in a photograph of a large emmetropic eye than of a small emmetropic eye One type of camera makes certain compensations for refractive power, but this modification is intended to give constant size of field—not to compensate accurately for differences in refractive power No doubt in time these difficulties will be surmounted, but meanwhile we are a long way from achieving the perfect retinal camera

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1 Boort, H J J van Warmoltz, N M , Winkelman J E *Med & Biol Illustr* 1956, 4, 166
2 Meyer-Schwickerath G , Niesel, P *Photogr u Forsch* 1954, 6, 73
3 Loisillier, F *Arch Ophtal , Paris,* 1955, 15, 395
4 Hansell P , Beeson E J G *Brit J Ophthal* 1953, 37, 65
5 Hansell P *Med & Biol Illustr* 1957, 7, 91
6 Leishman R *Brit J Ophthal* 1957, 41, 641

MEDICINE IN ASIA ORGANISATION AND EDUCATION

IN Europe there are about 930 people to every doctor, in Asia the corresponding figure is more than 6400, and in some parts of Asia it is higher still—e g , over 70,000 in Indonesia and over 174,000 in Nepal But medical services are expanding fast before the late war there was but a handful of health centres in all Asia, but at the end of last year there were 7251 multi-purpose centres, excluding those in Japan (about 900) and China As Dr John B Grant points out in a report to the Rockefeller Foundation, such swift expansion causes difficulties in organisation, and inquiries are needed into what administrative machinery should be provided Lack of such inquiries, he says, is leading to administrative chaos in several countries As the best solution to the problems of organisation, he suggests a regionalisation of services on the lines lately begun in Puerto Rico[1]

Even more important is the shortage of doctors and health workers, and the fact that the graduates of many of the present medical schools (and other training institutions) are not really competent to staff the new health centres—a situation necessitating hurried courses aimed at giving the graduates training in the work they will do The purpose of undergraduate medical education, as Dr Grant sees it, is

> "To train an undifferentiated physician, competent to undertake general practice in his own community A large part of general practice in Asian countries is to staff and administer peripheral health centers The undergraduate medical curriculum of these countries is patterned on curricula of the United States and of the United Kingdom and entirely unoriented towards the health care service demands of these Asian countries It is true that the quality of medical education should not in any way be endangered by service pressures However, undergraduate medical education unoriented towards local needs is not quality education in the true sense"

It will not be easy, he says, to provide such education, experiments must be made in the extension of training beyond the universities' own ward and outpatient services into the community The universities must control their own community agencies, such as health centres, where the medical clerk and the intern can have facilities to train themselves in what increasingly is becoming general practice in their community But this must await the establishment of accepted standards of service in these centres—as yet there are none

In some countries the necessary expansion and change is held up, not by lack of funds, but by conservatism in the faculty Dr Grant cites Calcutta, where none of the four medical schools has established a chair of social and preventive medicine, despite the Government's offer to pay the whole capital cost and half the running costs for five years The solution, he thinks, is for each country to use its *new* medical colleges to establish a progressive curriculum, to serve as an example to the others A successful demonstration is the best means of persuasion The All India Institute of Medical Sciences, founded two years ago in New Delhi, will, it is hoped, provide such a demonstration Moreover, each country needs an agency, representing the Ministries of Health and of Education, to plan medical education and serve as a liaison between the Government and the peripheral institutions Such an agency could disseminate new ideas and recommendations in medical education

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1 See *Lancet*, Feb 22, 1958, p 440

Congresses

INTERNAL MEDICINE

The fifth congress of the International Society of Internal Medicine was held in Philadelphia on April 23–26, under the presidency of Dr T Grier Miller We publish below short accounts of some of the contributions to the congress

Medical Treatment of Hypertension

Prof R W Wilkins (Boston) claimed good results from medical treatment of hypertension in addition to rauwolfia, veratrum, hydrallazine, and ganglion-blocking agents, chlorothiazide was proving successful He regarded its chief use as that of a hypotensive drug, in combination with other agents Usually smaller doses could be employed he often started with 125 mg t d s, and found it unnecessary to exceed 750 mg daily Side-effects in 500 patients had included potassium depletion in nearly 40% (requiring replacement), nitrogen retention, sodium depletion, alkalosis, and collapse Potassium depletion was the most frequent and important, sometimes causing cardiac arrhythmias 5 deaths had occurred in patients receiving chlorothiazide, although it was impossible to be certain whether the drug was responsible The reason for its hypotensive action was unknown He also warned against the production of angina by hydrallazine due, to increased cardiac output, and by ganglion-blocking drugs due to poor coronary flow

Diet and Serum-cholesterol

Prof H Malmros (Lund) reported that the serum-cholesterol level could be lowered if ethyl linoleate was added to the diet, and butter fat was also excluded No lowering was seen if butter fat continued to be taken Milk fat and hydrogenated whale or coconut oil added to diet caused a rise in cholesterol Professor Malmros had treated patients with familial xanthomatosis over long periods with diets containing no milk or butter but with substitution of corn oil the cholesterol invariably fell He advocated this diet in coronary-artery disease

E C G Changes in Cardiac Infarction

Dr A Myasnikov (Moscow) reported that application of a piece of necrotic muscle to the normal heart in frogs and rabbits produced cardiographic changes of acute myocardial infarction These changes were due to the migration of potassium ions from necrotic muscle into adjacent zones, and it was suggested that the changes in cardiac infarction were derived from the zone surrounding infarction rather than from the damaged muscle itself

Anticoagulant Therapy

Dr J W Keyes (Detroit) emphasised that the maximum benefit of long-term anticoagulant therapy after cardiac infarction was seen in the first 18 months, after which the death-rates of treated and untreated groups became very similar, although the mortality remained higher in the untreated group If long-term anticoagulants were to be discontinued it was wise to wait until 18 months after an infarction He doubted whether patients receiving anticoagulants for rheumatic auricular fibrillation with emboli could ever safely discontinue therapy

Dr P E Lucomsky (Moscow) regarded anticoagulants as obligatory in all cases of myocardial infarction, and they should be continued for 6 weeks He also advised anticoagulants for severe and repeated angina

Dr M Wiener (New York City) said there was no particular advantage of any one hypoprothrombinæmic drug over any of the others, and the choice depended on whether a rapid, intermediate, or long-acting preparation was required

Dr T Astrup (Copenhagen) pointed out that anticoagulants in cases of cerebral thrombosis might carry a greater risk of hæmorrhage into the infarcted area; since he had found the meninges to possess greater fibrinolytic activity than any other tissue

Dr F Koller (Zürich) regarded the Quick one-stage prothrombin estimation as unsatisfactory, since it did not give a true indication of what was happening Factor IX could not be measured, but Stewart's factor could be and showed a discrepancy with the Quick test Stewart's factor more accurately reflected the tendency to hæmorrhage than prothrombin estimation, and may prove a more reliable guide

Dr S Cosgriff (New York) advised intermittent heparin whenever the prothrombin-time fell below the therapeutic range He also recommended oral vitamin K_1 if the prothrombin-time rose above 35 sec

Dr Irving Wright (New York) had found that thrombotic episodes were more common than expected following sudden cessation of therapy, and although statistical evidence was not available he had the impression that slow stoppage prevented thrombosis

Insulin and Dehydration

Dr J Roguski (Poznan) reported that small doses of insulin hastened rehydration in cellular dehydration caused by vomiting, but it might give rise to hypokalæmia Mental disturbance after drainage of ascites due to hepatic cirrhosis was usually the result of hypokalæmia with or without hyponatræmia, and a similar picture could occur after long-continued treatment of heart-failure with low-sodium diet and mercurial diuretics

Intracardiac Thrombi

Dr H Berg (Hamburg-Eppendorf) reported 4 cases of intracardiac thrombi diagnosed during life by auscultation over the carotid artery Murmurs developed under observation which were either rough systolic murmurs or vibrating murmurs which changed at different times and were often intermittent The 4 cases were proved at necropsy

17-Hydroxycorticosteroids and Liver Disease

Dr G Bossa (Naples) described estimations of 17-hydroxycorticosteroid levels in the blood of dogs and of patients with mitral stenosis and with hepatic cirrhosis He concluded that liver disease interfered with the normal breakdown of 17-hydroxycorticosteroids, but the blood-level in such patients was unusually low, probably the result of diminished glucocorticoid secretion by the adrenal cortex

Benign Orthostatic Albuminuria

Dr E Lowgren (Vasteras, Sweden) suggested, as a result of electrophoretic study of the blood and urine, a new mechanism for benign orthostatic albuminuria The constant electrophoretic pattern, resembling that of lymph, seemed to indicate that the albuminuria was due to post-tubular lymphuria and was not the result of glomerular infiltration

Corticotrophin as Diuretic

Dr M H Rigoli (Buenos Aires) reported the production of diuresis by intravenous corticotrophin in patients with acute tubular insufficiency, manifested as anuria or oliguria The diuresis always occurred within 24 hours and did not seem to be a coincidental spontaneous diuresis, since it was produced irrespective of the day of the disease on which corticotrophin was administered He could not explain his observations The dose used was 50 mg in 24 hours

Symposium on Hæmatology

Dr J S Richardson (London) said that leukæmia could be preceded by a state, occasionally lasting some months, which might present as aplastic anæmia, leucopenia, thrombocytopenia, or pancytopenia (hypersplenism). Occasionally macrocytic anæmia might be found. The bone-marrow did not at this stage suggest leukæmia, but some months later leukæmic cells appeared. The correct diagnosis might be suggested if an enlarging liver was encountered during the preleukæmic phase. It was tempting to believe that this condition had a multiple ætiology, but invariably progressed to leukæmia.

Dr LUIGI VILLA (Milan) reported differences in the physical properties of desoxypentosenucloid acids in the nuclei of normal and leukæmic cells. These differences appeared to be linked with the physical state of the D.N.A. molecules.

Dr M. ROMER (Caracas) had studied the red cells in iron-deficiency anæmia and concluded that microcytosis developed first, followed by hypochromia, and finally a fall in the number of total red cells.

Prof HISAO MORITA (Tokyo) reported that he had established the existence of 4 blood-groups in human platelets corresponding to the ABO system. He also described a method of measuring platelet fragility.

Dr CARL MOORE (St Louis) emphasised that normally only 10% of food iron was absorbed, but this may be doubled in iron-deficient subjects. Ascorbic acid considerably enhanced absorption. In men iron-deficiency anæmia theoretically would take about 6 years to develop on an iron-free diet in the absence of bleeding, but only very small amounts lost continually would cause anæmia.

Arthritis and Rheumatism

Dr R. L. BLACK (Bethesda) said that steroid therapy did not replace rest and physiotherapy, but when indicated should be used in the lowest possible dose. He had followed 59 patients with rheumatoid arthritis receiving prednisone for up to 3½ years. 8 patients died, 2 from fulminating infections and 2 from gastrointestinal hæmorrhage; the remaining 4 deaths may have been unrelated. 15 patients developed peptic ulcers, and higher doses seemed more likely to produce ulcers. 9 patients developed fractures, usually vertebral. Only 3 patients with serious complications received less than 15 mg daily. He believed that vascular lesions similar to polyarteritis nodosa were an integral part of rheumatoid arthritis, and could be found in patients who never received steroids.

Dr D. LONG (London) described experiments on guinea-pigs showing that thyroid activity was considerably increased if an antigen was injected into a hypersensitive animal. Thyroxine increased the severity of allergic reactions in guineapigs, and since these reacted similarly to monkeys and man, he speculated on the possibility of hyperthyroidism being the underlying basis for human hypersensitivity to streptococcal allergens. He pointed out that when thyroidectomy had been carried out in the past in patients with rheumatic fever, the symptoms had abated strikingly.

Prof NANNA SVARTZ (Stockholm) reported that a factor capable of agglutinating sensitised erythrocytes could be demonstrated in the serum of 85% of rheumatoid-arthritis patients. This factor was precipitable in the cold, but hæmagglutinins in other collagen disorders remained in the supernatant fluid. Ultracentrifugation established that this factor was present in fractions containing macroglobulins.

During a panel discussion Dr LONG thought that clinical trials comparing cortisone and aspirin were a waste of time, and urged research into their mode of action as a first step. He said that much of the earlier work on infection in animals receiving steroids was invalid owing to species difference, and there was little evidence of true anti-inflammatory effect apart from depression of delayed tuberculin sensitivity.

Dr SCULL advocated large doses of steroids, and he had found different patients responded better to different compounds. He did not believe there was any increase in intercurrent infection among patients on steroids. He recommended gold for ambulant patients on steroids initially, until an effect from gold was obtained, but he did not think there was any synergistic effect. He had found improvement in patients receiving chloraginine for rheumatoid arthritis.

Dr R. H. FREYBURG (New York) preferred not to exceed 15 mg of prednisone or equivalent daily in males and 10 mg in females. He has been disappointed with antimalarial drugs in rheumatoid arthritis. For acute gout he recommended colchicine, phenylbutazone, and steroids in that order of preference.

Stress and Cerebral Function

Dr LORING CHAPMAN (New York) found that patients with chronic diseases causing prolonged stress, such as peptic ulcer or ulcerative colitis, did not show any impairment of the highest integrative functions of the brain if there was no disturbance of behaviour or mood. In patients where there was such disturbance severe loss of higher functions was found.

Aphasia and Writing

Dr V. G. VON MUNDY (Knittelfeld) reported that aphasia as a result of hemiplegia in children who had not yet learned to write was slight and rapidly recoverable. He suggested that the unilateral development of the speech centre was related to the use of one hand for writing. Adults who were illiterate retained symmetrical speech centres, and in them aphasia was also slight or absent.

Obliterative Atherosclerosis

Dr K. GIBINSKI (Bytom, Poland) reported comparisons between venous blood obtained from the lower limbs of subjects with obliterative atherosclerosis and blood from upper limbs. No significant difference was found in content of proteins, lipoproteins, or cholesterol. Serum-glutamic-pyruvic-transaminase was higher in lower-limb blood, and there was a marked decrease in serum-proteolytic activity. There seemed to be some correlation between this decrease of proteolytic activity and the severity of the disease.

Lipids and Coagulation

Dr E. SZCZEKLIK (Warsaw) reported that the serum-prothrombin level, using Quick's one-stage method, and level of factor VII accompanied the rise of serum-cholesterol in early atherosclerosis, although the phospholipoids and C/P ratio remained normal. In later atherosclerosis an increase in C/P ratio occurred and in addition to increased prothrombin and factor-VII levels, there was delayed thrombin inactivation and protraction of fibrinolysis time.

Splenomegalies of Banti Type

Dr C. CRUZ LIMA (Rio de Janeiro) found that congestive changes with thromboses in the spleen, and reticular proliferation with endophlebitis in the liver could be produced in dogs by giving horse-serum for periods up to 5 months and inducing sensitivity. He considered the picture similar in many respects to Banti's syndrome in man, and suggested that hypersensitivity might be one cause.

Hæmoptysis in Older Men

Prof KATHERINE BOUCOT (Philadelphia) reported diagnostic and follow-up studies in a group of 395 men over 45 years who had hæmoptysis. In 43% no cause could be found, 33% had lower respiratory infections, 9% bronchial neoplasms, and in 9% the cause was cardiovascular. Only 18% who had hæmoptysis as an isolated symptom were found to have severe disease. She had not seen bronchial carcinoma in men who smoked for less than 20 years, and occasional smokers had to smoke for 40 years or more before developing a carcinoma.

Pretibial Myxœdema

Dr OTTO WEGELIUS (Helsingfors) reported 21 patients with pretibial myxœdema in association with exophthalmos. The peak incidence was between 40 and 60 years, and women greatly outnumbered men 15 patients had received previous treatment for thyrotoxicosis, and pretibial myxœdema might develop as long as 2 years afterwards As a result of animal experiments he attributed the condition to the action of thyrotrophic hormone upon the connective tissues of a hypothyroid subject in any area of slight dependent œdema—for instance, the lower legs and pretibial region

Ventriculography in Mitral Disease

Dr J F Uricchio (Philadelphia) described the results of left ventriculography in 42 patients with mitral-valve disease A needle was inserted directly beneath the xiphoid Patients with significant mitral incompetence showed considerable opacification of the left atrium, and this method enabled an accurate diagnosis to be made Arrhythmias and conduction defects arose at the time of injection in some patients there had been 2 deaths, 1 from cardiac arrest, and the other from direct injection into the myocardium

Depression of Serum Freezing-point

Dr E Olmstead (Milwaukee) described the value of the depression of the serum freezing-point in some clinical syndromes In normal persons this figure was very constant and required only 2 ml of plasma for its estimation Most of the depression was due to the plasma-sodium In overhydration the freezing-point was above normal, but it was lowered in primary water loss In salt depletion the value remained normal despite a low serum-sodium, and in primary renal impairment the freezing-point was lowered further, despite a low or normal serum-sodium This was probably the result of the retention of other metabolites

Radiation Nephritis

Dr R W Luxton (Manchester) discussed radiation nephritis in 53 patients who had had renal disease after abdominal irradiation Acute radiation nephritis may come on 8–12 months afterwards recovery could take place, although the kidneys were permanently small Malignant hypertension may develop during the acute stage and recovery could still take place It may also develop slowly up to 4 years later

Treatment of Nephrosis

Dr H C Goodman (Bethesda) reported results of steroid treatment of 34 patients with nephrotic syndrome There might be complete remission, complete remission with normal serum-proteins but residual albuminuria, partial remission, or none 40 mg of prednisolone or equivalent was given daily for a month A good response, when it followed, invariably did so within 10–14 days In the absence of a response, steroid withdrawal might sometimes cause diuresis Relapses were always followed by second remission with a further course of steroids In only 1 out of 7 patients did chloraquine seem to have any beneficial effect

Paroxysmal Ventricular Tachycardia

Dr G R Herrmann (Galveston, Texas) had analysed 175 consecutive cases of paroxysmal supraventricular tachycardia, and found approximately 75% to be associated with organic heart-disease, and a third showed partial auriculoventricular block, usually the result of digitalis Associated heart-disease was commoner in older patients and was usually ischæmic or hypertensive When tachycardia complicated recent infarction the prognosis was poor Tachycardia was poorly tolerated in presence of organic heart-disease, and he recommended rapid digitalisation, if none had been given previously It was also useful in preventing attacks There were no significant differences in rate between the groups

Hydrocortisone Metabolism in Hyperthyroidism and Myxœdema

Dr R E Peterson (Bethesda) reported studies on endogenous hydrocortisone in thyrotoxicosis and myxœdema Hydrocortisone was metabolised far quicker in thyrotoxicosis, and synthesis was more rapid The reverse was true in myxœdema These findings may depend upon an increase and decrease respectively of activity in the liver He suggested that severe myxœdema might be accompanied by a relative adrenal insufficiency

Symposium on Tuberculosis

At this symposium sponsored by the American Trudeau Society Dr R H Ebert (Cleveland) said that all antituberculous drugs, if given alone, led to resistance of organisms, and combined therapy over prolonged periods without interruption was to be preferred All drugs had toxic effects which had to be borne in mind About 50% of all patients destroyed isoniazid very quickly, but this was perhaps prevented by concomitant P A S Large doses of isoniazid in excess of 300 mg daily were now known to be tolerated safely if pyridoxin were given simultaneously He thought steroids had a definite place in the treatment of meningitis, combined with antibiotics

Dr Norman Wilson (Boston) said that the only indication for surgery was the failure or anticipated failure of medical treatment to control disease permanently Resection was indicated for destroyed units of lung or persistent caseation, particularly in inspissated cavities Thoracoplasty had a definite place in cases where there was extensive nodulation or fibrosis elsewhere in the lung, and especially in cases with open cavities and positive sputum, usually resistant to drugs Antibiotics had made possible less extensive thoracoplasties, and he advised a separate approach to each individual case

Carcinomatous Myoneuropathies

Sir Russell Brain (London) described 42 examples of carcinomatous myoneuropathy, of which 75% were associated with bronchial carcinoma Their appearance may antedate the detection of the primary tumour by up to 3 years, and although they often responded to its removal, this was by no means invariable Occasionally the syndrome developed after the primary growth had been removed There were varied syndromes, including cerebellar degeneration, sensory neuropathy, and involvement of pyramidal tracts and posterior columns Dementia could accompany these, and in a third of Sir Russell's cases a true myopathy alone was observed Pathologically, there was considerable degeneration of the affected area, with perivascular cuffing The exact mechanism was still unknown

Abacterial Subacute Endocarditis

Dr C Jiménez-Diaz (Madrid) said that abacterial subacute endocarditis presented a similar picture to the bacterial form, although the spleen was characteristically very large and the sedimentation-rate unusually high The plasma showed considerable hypergammaglobulinæmia, blood-cultures were always negative, and although histologically the lesions were identical with bacterial endocaroditis, postmortem cultures of the valves never showed bacteria He believed that the condition was not of bacterial origin, but the result of altered globulins converting the plasma into an autonoxious agent, and that rheumatic, Libman-Sacks, and other types of endocarditis might have a similar basis

Oral Hypoglycæmic Agents

Dr Charles Best (Toronto) said that at least two-thirds of diabetics who had had tolbutamide had continued to take this satisfactorily There was convincing evidence that oral hypoglycæmic drugs increased plasma-insulin and therefore increased pancreatic insulin production Sugar production by the liver was decreased In his department pancreatectomised dogs receiving tolbutamide constantly showed a rise in serum-alkaline-phosphatase and decrease in prothrombin The animals dying had all shown characteristic changes in the Kupfer cells

Symposium on Cardiovascular Surgery

Dr Alfred Blalock (Baltimore) reported that the survival-rate in dogs after ligating the descending branch of the left coronary artery was 30% in normals, but increased to 80% if omentopexy had been previously performed to increase collateral circulation. Experiments in dogs showed that the carotid artery transplanted into the myocardium remained patent in 90%, though the amount of fluid which could be perfused through it was very small. After this procedure the survival-rate following coronary ligation increased to 64%, but internal mammary ligation conferred no protection. He thought endarterectomy had a sound basis judged by necropsy experiments, since the perfusion-rate subsequently had much increased. He felt operation should be advised when pain continued and could not be controlled by medical means, and he used the Beck 1 operation, though the results were similar irrespective of the type of procedure.

Dr C. W. Lillehei (Minneapolis) said that open heart surgery now made it possible to deal with mitral and aortic incompetence. He emphasised that calcium was seldom found in the valves of mitral incompetence, nor was the annulus usually dilated, so that pathologically such valves were well suited for surgery. In such cases he repaired the valve by inserting ivalon strips beneath the cusps. Aortic incompetence could be repaired by inserting a new leaflet, and also a plastic valve beneath the coronary orifices. It was useless to employ open heart surgery unless the surgeon could work on the valve for at least 30–40 minutes, and consequently retrograde perfusion through the coronary sinus was used. Open surgery was suitable for mitral stenosis in cases with marked disability indicating gross valvular deformity in those with a history of emboli or with mitral incompetence or re-stenosis, and in all children.

Dr Robert Linton (Boston) said that indications for vascular grafts include obliterative arterial disease, aneurysms, arterial injury, tumour involvement of vessels, and congenital abnormalities. He did not now employ aortography because of increased risks, but he used arteriograms of limbs. He emphasised the successful use of end-to-end saphenous by-pass for localised obstruction in the lower limbs, which was the method of choice, and failing this he regarded thromboendarterectomy as a sound procedure. He did not use synthetic prostheses for replacement in the lower limbs owing to the risk of thrombosis, but he regarded this as very suitable for replacement of aortic lesions, followed by arterial homografts.

Medical Aspects of Cancer

For the first time in the history of the congress, a session was devoted to cancer. Prof Lowell Coggeshall (Chicago) mentioned that in America $30,000,000 was devoted annually to cancer research and to helping cancer sufferers. The internist could help at all stages—diagnosis, treatment and the management of the long-term patient. Mr E. Cuyler Hammond, SC.D. (New York), showed that the crude cancer-rate was increasing in all civilised countries. The abolition of other diseases augmented the rate, but did not explain the gross increase in carcinoma of the lung in men and in leukæmia in both sexes. Mortality from carcinoma of the rectum had fallen, probably due to earlier treatment, that of the stomach had fallen, but probably surgery had no part in this fall. The decline of gastric carcinoma was greater in the United States than in England. He quoted a survey in Connecticut which showed that the five-year survival-rate for cancer from 1935–40, 1941–6, 1947–51, was 19, 22, 25% for males and 29, 35, 38% for females. This rise was greatest for patients with growths of the rectum and colon, and for those with prostatic and uterine cancer. In the United States the present annual death-rate was 211,000 and it was estimated that this would rise to 322,000 in 2000 A.D., even if progress of treatment was maintained at the present rate. If coronary-artery thrombosis was abolished the cancer figure would be 566,000.

Prof E. Day (New York) concentrated his hopes of early diagnosis on periodic examination of available sites. A history of anæmia, loss of weight, or inertia and a family history might be precedents but the examination was all-important. He estimated that 28,800—i.e., 80% of the 36,000 who die yearly of rectal or colonic cancer—might be saved and that 10% of those who die of lung cancer might be saved by annual lung X-ray examinations, but he gave no figures to support these hopes. He was emphatic that digital rectal examination, never to be neglected, was inadequate; in 125 patients with carcinoma or with a carcinomatous polyp of the rectum, only 17 were detectable by digital examination, whereas the sigmoidoscope revealed all.

Dr D. C. Dahlin (Rochester) showed the value of cervical scrapes for diagnosing carcinoma of the cervix uteri. He was not in favour of similar investigations for carcinoma of the body, 90% of which caused post-menopausal bleeding and 80% of cases were amenable to surgery.

Prof R. H. Chamberlain (Philadelphia) and Dr Shields Warren (Boston) were modest in their claims for deep X-ray therapy and for isotopes. It was hoped that increased oxygen saturation of some tissues might increase the effectivity of radiation. Palliation was usually all that was obtained, and this was illustrated by the fact that no person with disseminated thyroid carcinoma had been cured. ^{32}P was very useful for polycythæmia vera but for leukæmia it was less effective than deep X rays. It was occasionally of value in plasma-celled myeloma causing bone pain.

Dr S. G. Taylor (Chicago) said the long-term survival patient often had inevitable pain, relieved by leading an active physical or mental life, by freedom from conflicts, by good nights' sleep. Simple non-narcotic analgesics helped at first but later there was no perfect drug. Narcotics combined with narcotic antagonists had failed to establish their claim. Addiction was uncommon. For many adrenalectomy and hypophysectomy added a few years of tolerable life.

Dr J. E. Eckenhoff (Philadelphia) discussed the relief of pain. Besides the standard measures, injection of the cœliac ganglion by the posterior approach was often effective for carcinoma of the pancreas. A preliminary injection of procaine, if helpful, was followed by an injection of 10% æquous phenol and gave benefit for 3–4 months. Injection of somatic nerves often helped incurable pain but produced neuritis in 20%. Finally, Dr A. M. Sutherland (New York) spoke of the psychological problems. Anxiety, fears, delusions, paranoic tendencies, and compulsive practices could all be helped. No word was said about smoking.

Poliomyelitis

Prof Jonas Salk (Pittsburgh) said that workers from many nations had contributed the foundation stones on which present progress depended. Killed vaccine with types 1, 2, and 3 virus produced antibody, and two doses given at short intervals produced a definite rise which was almost doubled by a third dose given seven months later. Although the titre fell, it remained slightly higher than it was before the injection of the third dose and remained so for 4 years. 0.1 ml. of vaccine intradermally further enhanced immunity and was a satisfactory antigen. A fourth dose was advisable as it helped approximately 10% who had not developed a satisfactory antibody level after three doses. At present he was not prepared to say dogmatically whether the value of vaccination lay in producing a hypersensitivity immune reaction.

Dr H. M. Gelfand (New Orleans) studied 157 families, each of whom had a neonate in it. Infection with poliomyelitis usually occurred very early, 70% being infected in 7 months and 90% in 30 months. Of 105 families affected, 33 had type 1, 35 type 2, and 37 types 3. Minor illnesses occurred but no paralysis. After two years, Salk vaccination was introduced and minor infections diminished. Virus excretion in the stools was less in the vaccinated. His experiments suggest that vaccination did not influence poliovirus dissemination.

Dr Hilary Koprowski (Philadelphia) described how the poliomyelitis virus had been attenuated by passage through insusceptible hosts. After 28 mice adaptations it was given orally to 3 children, having been proved non-pathogenic for monkeys Later it was given to many others, in two doses with a month's interval and later a third dose at 15 to 30 months' interval Passage through human individuals did not restore the pathogenicity as judged by injecting large doses into monkeys' brains It therefore appeared that a safe living vaccine devoid of pathogenic power but of rich antigenic capability was being developed

Symposium on Gastroenterology

Dr W L Palmer (Chicago) discussed exfoliative cytology in the diagnosis of cancer of the digestive tract Lavage material from 151 patients showed distinctive cells in 66 out of 69 with carcinoma, compared with 55 suggestive X-rays 2 with œsophagitis were misdiagnosed Among 871 examinations, 125 of 131 carcinomas of the stomach were diagnosed X-rays diagnosed 81 correctly, 27 as suspicious, and 23 as normal Cytological interpretation of material from the pancreatic and biliary ducts was difficult, but in 33 of 55 proven cases malignant cells were recovered 301 examinations were negative In 183 suspected cases of colonic carcinoma, 36 of 38 proved cases had malignant cells Barium enema showed carcinoma in 28, it was normal in 5 and questionable in 5

Dr C A Clarke and Dr R B McConnell (Liverpool) demonstrated how people with blood-group O in many parts of the world were more liable to suffer from duodenal ulcer No satisfactory reason could be given

Prof A C Frazer (Birmingham) discussed the differential diagnosis of steatorrhœa He emphasised the importance of a gluten-free diet in the treatment of patients intolerant of gluten, proof of intolerance was given by a relapse when gluten was given experimentally to patients previously on a gluten-free diet This treatment was preferable to steroid therapy, which had a use in emergency treatment

Cardiac and Vascular Diseases

Prof Robert L Levy (New York) compared a group of 50 cases of myocardial infarction treated with adequate anticoagulant therapy with a similar group receiving no anticoagulants There was a 17% error of diagnosis in both groups Mural thrombi, pulmonary emboli, and systemic emboli were equally common in both groups 3 patients in the treated group died of hæmorrhage The incidence of cardiac rupture in 557 cases from the literature and Professor Levy's personal experience was 4% in untreated and 12% in those treated with adequate anticoagulant therapy

Dr Stig Radner (Lund) described central aortic pressure curves and left atrial pressure curves obtained by needle puncture through the suprasternal notch During the Valsalva manœuvre and in fainting the aortic curve was characterised by a very sharp upstroke and a double notch on the downstroke Aortic stenosis was characterised by a slow upstroke on the aortic pulse and a presystolic peak in the left atrial pulse

Prof Isaac Starr (Philadelphia), in an appraisal of the ballistocardiogram, emphasised the need for rigidly standard conditions before assessing the amplitude of the main deflections The abnormal form of some ballistocardiographic tracings had been simulated by pressure injections into the great vessels in the cadaver

Dr John J Sayen, Mr W F Sheldon, and Mr George Pierce (Philadelphia) described the changes in the myocardium of dogs following ligation of a medium branch of a coronary artery In the affected area oxygen tension fell rapidly and muscle contraction became abnormal Breathing oxygen and infusing noradrenaline raised oxygen tension nearly to normal and improved contraction in the ischæmic muscle

Prof G E Burch and Dr Lawrence Golden (Tulane) recorded spatial vector cardiograms from 233 clinically normal subjects Distortion of the QRS vectors was seen when the conventional ECG was normal Such distortions became commoner with advancing age, rising from 22% in the third decade to 68% in the sixth decade

Prof Herbert L Ratcliffe and Mr Theodore G Yerasimides (Philadelphia) found an increasing incidence, in recent decades, of arteriosclerosis in birds and mammals at the Philadelphia Zoo This was not related to increased longevity nor to a higher dietary intake of fat Social pressure and group conflict among the animals were possibl explanations

Effect of Rubefacients

Dr F A Elliott (London) described changes in blood flow induced by rubefacient agents After the production of an intense cutaneous erythema of the thigh, the temperature of the feet rose in 17 out of 30 patients with arterial disease of the legs Effort tolerance was increased tenfold in some cases of angina after erythema of the chest wall had been induced, and a rise in cerebrospinal-fluid pressure was recorded in 9 out of 12 patients with cerebral infarction whose necks were made erythematous Atropine and sympathectomy abolished this effect A cholinergic efferent nerve pathway was postulated

Steroid Therapy for Psoriatic Arthritis

Dr J L Hollander (Philadelphia) and his colleagues had used the steroid triamcinolone (delta-9-alpha-fluoro-16-alpha hydroxyhydrocortisone) in psoriatic arthritis Of 17 patients on 8–16 mg daily, 11 showed almost complete healing of skin lesions Improvement in the arthritis resembled that produced by prednisone Cessation of triamcinolone therapy resulted in prompt return of psoriasis Side-effects of the drug, especially anorexia, were common

Pulmonary Hypertension

Dr D S Short (London) described 70 post mortem pulmonary ateriograms in controls and in cases of pulmonary hypertension Abnormal arteriograms were obtained in all cases of pulmonary hypertension, the changes being most striking in the smaller vessels Some vessels were completely obstructed and abnormal communicating vessels were then found There was a generalised diffuse narrowing of vessels of less than 1 mm diameter The narrowing was due to permanent muscular contracture, a hypersensitivity of the vessels to an initially raised pressure

Primary Biliary Cirrhosis

Dr Albert Snell (Palo Alto, California) said that both the nutritional state of the patient and the metabolic functions of the liver were well preserved until late in the course of primary biliary cirrhosis There was a characteristic biochemical defect, in which the serum lipids, bilirubin, and alkaline-phosphatase levels were raised The presence or absence of cutaneous xanthomas depended on the serum-lipid level Prolonged T-tube drainage of the bile passages might lower bilirubin and lipid levels and relieve pruritus, without conferring other benefit Continuous or intermittent therapy with adrenocortical steroids had helped some patients Preparations of linoleic acid (to lower serum-lipid levels) had been disappointing, though symptoms had sometimes been relieved

Uses of the Miller-Abbott Tube

Dr T E Machella (Philadelphia) discussed the uses of this tube in the diagnosis and treatment of gastrointestinal diseases They included the collection of œsophageal washings for examination for the presence of malignant cells, collection of duodenal juice for microscopic examination of bile, chemical analysis for the amount and concentration of pancreatic enzymes, and examination for the presence of exfoliated malignant cells, obturation of the duodenum as an aid to cholangiography, location of the site of intestinal bleeding, localisation of a point of partial intestinal obstruction, radiological display of small intestinal lesions, and the reproduction of distension types of pain at the suspected site of origin by air insufflation of a balloon In treatment, the tube could be used to deflate the bowel in ileus, to protect sutures in intestinal anastomoses, and as a " medical ileostomy " to prevent small intestinal contents from reaching the colon in patients with ulcerative colitis

Special Articles

SYRINGE SERVICE IN THE SMALL HOSPITAL

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INCREASING importance is being attached to the setting up and functioning of syringe services in hospitals. Various methods have been described, but these have been suitable only for very large units or groups of hospitals. The large initial capital outlay and the high running costs might discourage small units from attempting to set up a service, so our experience over the past three years may be of interest to other hospitals of similar size.

EQUIPMENT

Ovens.—It is agreed that boiling is ineffective, and therefore hot-air sterilisation is obligatory. We use two ovens—a small one in the admission unit, and a larger one in the laboratory for the remainder of the hospital. They cost £40 and £160 respectively and are thermostatically controlled.

Containers.—We tried glass test-tubes with adhesive-tape sealing but abandoned them because of difficulties in unsealing and because breakages of both container and syringe were high. We found also that metal containers were not ideal: they took up a lot of space and rolled about, and their contents could not be seen. Material used for packing was apt to char at the necessary temperature, and sealing was difficult. We have now adopted 'Cellophane' envelopes (McCartney 1951) and consider this the ideal method. The envelopes are brittle after heating and should be allowed to cool for an hour before being touched.

Syringes are all glass with metal nozzle able to withstand sterilisation at 160°C in the hot-air oven, in the following sizes: 2 ml., 5 ml., and 10 ml.

Needles are stainless-steel hypodermic nos. 12 and 20, intradermal, and serum no. 1.

Cellophane envelopes in the following sizes: $7 \times 2^1/_2 \times {}^3/_4$ in. flap (syringes), $3^1/_4 \times 1 \times {}^3/_4$ in. flap (needles). The two expendable envelopes together cost 1·025*d*.

Miscellaneous.—Cellophane adhesive tape 1-in. rolls, suitable wire baskets and trays for the hot-air oven, lubricating solution (liquid paraffin levis *B.P.* 1 part, methylated ether 4 parts).

METHOD

The syringes are cleaned in the wards by washing in water to which a suitable cleanser has been added. 'Sterovol' is particularly suitable, especially where specimens of blood have to be taken, because it does not foam and, on drying, does not leave a film on the glass. Some other cleansing agents tend to cause a film, which is liable to hæmolyse the blood. We have obtained every cooperation from the wards because the advantages of this system have been so obvious.

Clean syringes are returned to the laboratory and placed on the shelf of a cooling hot-air oven, and this completes drying. The barrels and pistons are not interchangeable; when they are being dried off before sterilisation they are mounted in pairs on a special rack which we have designed with hollow pegs to hold the barrels and with Terry's clips mounted behind these pegs to hold the pistons. The syringes are then assembled, lubricated, and packed for sterilisation. Each batch is tested in the steriliser by means of a Browne's control tube, type 3, one tube being in each cageful of syringes. We have also tested occasional batches with cultures of *Bacillus subtilis*, a sporing bacillus. Batches of about 100 syringes are now taken and lubricated in the following manner: the piston is placed in a jar of lubricating solution up to a depth of $^1/_4$ in. and then inserted in the barrel, the piston being drawn up and down to ensure even distribution of the lubricant.

The syringes are now placed in the cellophane envelopes, and the flaps are sealed with cellophane tape, or by means of cellophane cement. The tape is cut in 3-in. lengths and stuck to the overside of the $^3/_4$-in. flap; this provides an overlap throughout and forms a complete seal.

The needles are packed in envelopes $3^1/_4 \times {}^3/_4$ in. and are protected by cellophane straws cut into suitable lengths. These are sealed in packets in the same way as the syringes. Occasionally three or more can be placed in one packet for use at electroconvulsion-therapy session with relaxants. The syringes are now placed upright in wire baskets, and the needles on suitable trays. The needles are examined each time for hooking and touched up (if necessary) on an Arkansas stone. If they are blunt they are collected and sent in batches for sharpening, which costs about 2*s.* a dozen.

Baskets and trays are placed in the hot-air oven, and the current is switched on. Sterilisation is achieved in the oven at 160°C for an hour.

The oven is allowed to cool completely before the syringes and needles are removed, when they can be handled and distributed safely.

The capacity of our present arrangements is probably 100 syringes a day, which is ample for our use. The admission unit is self-supporting. The staff are now competent to carry out the sterilisation after an initial period of instruction.

Complementary to the sterilising service has been the design and development of a piece of apparatus for freeing stuck pistons in the all-glass syringes used. No piece of apparatus at that time existed, and the idea and development has been solely the work of one of us (F. C. R.). It is designed on hydraulic principles and consists of a release adaptor similar to a double-ended Weinraud connection. On one side a small syringe is fitted and filled with water, and on the other side the stuck syringe. The pressure built up is sufficient to free any stuck syringe. This apparatus can be obtained from Messrs. Robert Whitelaw Ltd., Newcastle upon Tyne, at about 4*s.* each. Since it is so cheap it can be kept in the wards. In this hospital the problem of a stuck syringe no longer exists. Breakages averaged previously 20 a month and now rarely exceed 2 a month.

CONCLUSIONS AND SUMMARY

A simple and efficient syringe service suitable for the needs of a small hospital is described.

The capital outlay is small—certainly less than £200. There is no need for additional staff, and the running costs are low. The wastage through breakages and deterioration of equipment through repeated boiling in hard water is eliminated

The method can be applied also to sterilisation of other pieces of equipment—e g , forceps, scissors, and scalpels

Envelopes are obtainable from Clear View Ltd , Crouch Hall, London, N 8, 'Steroxol' cleaner from Messrs La Porte Chemicals, Luton, Beds , and the 'Klintex-Ralph' adaptor for releasing stuck syringes from Messrs Robert Whitelaw Ltd , Klintex House, Great North Road, Newcastle upon Tyne

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McCartney J E (1951) *Lancet*, i, 509

Nuffield Provincial Hospitals Trust (1957) The Planning and Organisation of Central Syringe Services London

POLIOMYELITIS VACCINATION

Medical Research Council Statement

LAST week the Medical Research Council issued the following statement about poliomyelitis vaccination

(1) The Medical Research Council have been asked by the Government to advise whether, in view of the present shortage of poliomyelitis vaccine, American or Canadian Salk vaccine which has satisfactorily passed safety tests and been licensed for issue in the country of origin should be made available for use in this country without first being subjected to the safety tests of the Medical Research Council

(2) The Council have made a full review of the current situation in the light of their responsibilities for safety testing poliomyelitis vaccine in this country They have given careful consideration to all the available evidence on the risks attending the use of the various poliomyelitis vaccines now being produced, on the risks in different circumstances of leaving a large number of children and others in special need of protection unvaccinated during the late spring and early summer months of this year, and to information on the amount of vaccine likely, under present arrangements, to become available for use in the next few months

(3) Three vaccines against poliomyelitis are available for consideration the British vaccine, imported American or Canadian vaccine that has passed British safety tests, and imported vaccine from the American or Canadian sources that has not been subjected to British safety tests The two former are now in use in this country the latter, at present, is not, although vaccine of this type has been used extensively elsewhere

(4) All poliomyelitis vaccine at present in use is made from three types of virus, types I, II and III In both the British and the American or Canadian vaccines, similar strains of the type II and type III viruses are used On the other hand, two different strains of type I virus are used The American and Canadian vaccines include the relatively virulent type I strain, known as Mahoney, the British vaccine, the much less virulent type I strain, known as Brunenders If, therefore, some of the virus failed to be inactivated in the course of manufacture, the British vaccine would be less likely to produce poliomyelitis on injection than would vaccines made from the Mahoney strain

It is the use of a type I strain of low virulence that makes the British vaccine the safest yet produced

(5) All vaccines are submitted to a series of safety tests at several stages before issue, both during and after manufacture, with the object of detecting any virus that has survived the process of inactivation Of necessity only samples of each batch of vaccine can be tested, and the possibility inevitably remains that in the untested part of the batch a few particles of live virus may still be present. It follows, therefore, that the greater the size and number of the samples tested, the smaller is the chance of any surviving virus remaining undetected and the greater the assurance that can be given regarding the safety of the vaccine

(6) If vaccine is submitted to an adequate number of safety tests of the full range now in use, there is little chance of contamination with live virus escaping detection If a few particles of live virus do escape, the effect on the safety of the vaccine will depend upon their virulence With the Brunenders strain of relatively low virulence used in the British vaccine, it is most improbable that any ill effects would follow inoculation, with the Mahoney strain, used in the American and Canadian vaccines, such a possibility could not be excluded with the same assurance

(7) It was because the more virulent Mahoney strain is used in the preparation of American and Canadian vaccine that the Medical Research Council, when recommending that vaccine should be imported from these countries to meet the shortage of poliomyelitis vaccine in the summer of 1957, linked that recommendation with the proviso that such vaccine should be submitted to further safety testing in this country in order to increase the safeguards against any particle of live virus of the virulent strain being present in the vaccine when issued

(8) Taking all these factors into account, the Medical Research Council believe that the three vaccines under consideration can be placed in the following order of safety

(*a*) Vaccine made according to the British formula that has successfully passed British safety tests,

(*b*) Imported vaccine from America and Canada that has successfully passed safety tests in the country of origin and also British safety tests,

(*c*) Imported vaccine from the same sources that has successfully passed safety tests and been licensed for issue in the country of origin

(9) After carefully weighing all the available evidence bearing on this complex problem, the Council are satisfied that the risk of producing paralytic poliomyelitis by injecting any one of these three vaccines is very slight and that a person inoculated with any one of them is substantially less likely to contract paralytic poliomyelitis than if he is left uninoculated. Nevertheless, no vaccine can be guaranteed to be wholly free from risk, and the preference should always be for the safest known vaccine

(10) The Council reaffirm their view that British type vaccine which has successfully passed British safety tests is the safest poliomyelitis vaccine known, that the only justifiable permanent policy is to use every endeavour to produce this in such quantities as to meet all the needs of this country, and that any policy which has recourse to less safe vaccines should, however slight the risk, only be regarded as temporary

Next in order of preference is imported vaccine that has passed successfully British safety tests as well as tests in the country of origin

Third is imported vaccine which, although it has successfully passed safety tests in the country of origin, has not been submitted to the further British tests carried out by the Medical Research Council in this country

(11) The present problem arises because supplies of British vaccine and imported vaccine that have passed British safety tests are together insufficient to meet requirements, and cannot become sufficient in time to present a substantial deficit during the summer months when the incidence of poliomyelitis may be expected to increase

(12) After carefully examining the present situation the Medical Research Council have concluded that, as it would appear to be impossible to overcome by any other means the deficit which will otherwise be inevitable during the summer months, it would be advisable as a temporary measure to issue American or Canadian vaccine which has not been submitted to British tests, provided that it has been tested and licensed for use in the country of origin

(13) *In proffering this opinion, however,* the Medical Research Council wish to stress their advice that the role of imported vaccine untested in this country should be limited to that of a temporary supplement to meet the present shortage At the same time every endeavour should be made to obtain the maximum possible supplies of British vaccine and imported vaccine which has satisfied both British tests and tests in the country of origin, so that, at the earliest possible moment, the need to use imported vaccine untested in this country will disappear The final aim should be to dispense with the need to use any vaccine containing the Mahoney strain

In England Now

A Running Commentary by Peripatetic Correspondents

THIS year the Royal Academy had the cooperation of the weather for the opening of its summer exhibition on May 2, and the blatantly bohemian and the firmly fashionable were able to make their improbable joint excursion to Burlington House without benefit of plastic mack or duffle coat. Turning to the pictures we found that the hanging committee had relaxed their policy of segregation and the moderns were no longer corralled in galleries VII and VIII There was as usual something for everyone, and the visitor could turn from Mr Merton's triptych of the *Countess of Dalkeith*—" Such a nice picture for her husband to have " as the kindly lady next to me said—to Mr Bratby's more turgid rendering of family life in *Nell and Jeremy Sandford* In gallery I the medical visitor will find *Lord Cohen of Birkenhead*, painted by Mr Harold Knight, sitting before a panelled background, alert and politely attentive, as he has sat in the chair at so many meetings In the same gallery hangs Mr B Fleetwood-Walker's portrait of *Professor Norman Capon*, kindly and quizzical, in muted scarlet academic gown with purple facings In gallery V it was pleasant to find a friend from the Medical Art Society, Dr Phoebus Tuttnauer's brilliantly coloured *Boats at Rest* lie on equally vivid orderly shingle Those with an eye for tomorrow as well as today will find in the architectural room drawings of the Middlesex Hospital Medical School and the new College of General Practitioners

* * *

The morning after my seven-year-old set the house on fire I arrived late at the hospital My hair was singed and the smoke had given me conjunctivitis, stomatitis, laryngitis, bronchitis, and the jitters The chief problem on my mind was how to ensure that the incident would not recur During the day's work I was offered all kinds of advice

A pædiatrician said that Johnny had obviously made a mistake, which was part of the natural process of growing up but personally I do not care to live so dangerously A physician (common-sense type) said that the Cautionary Tales and the story of Harriet and the Matches should be introduced, but these have long been part of the family's library A dermatologist said the boy should have his backside tanned, but Johnny's skin is exceptionally insensitive to physical violence Another physician (a born research-worker) said it showed an experimental mind which should be encouraged A patient, dependent and resentful, waited a long time to see me, and, to keep her quiet, was told the reason She said the boy should be shut away in a home—meaning that he would then be unable to delay her access to the doctor A psychiatrist who is analytically minded told me that the desire of a child to destroy his family by fire results from a deep-seated conflict requiring prolonged psychiatric treatment It had not occurred to me before that Johnny's fire might have been smaller rather than bigger than he intended, but after a moment's thought I dismissed the idea as ridiculous An administrator thought that a list should be made of all items destroyed and their cost deducted from pocket money I worked out that Johnny would still be paying when he comes of age A surgeon suggested that the boy himself should assist in the radical operation necessary to clear the affected area

When, full of thoughts, I returned home, my three-year-old daughter said " Johnny is naughty He lit a bonfire in the house He is very sorry " I think she was right On the hall table was a parcel addressed to me and untidily wrapped in newspaper Its label said THIS IS MY SEECRIT STOR YOU CAN HAV IT LOVE FROM JOHNNY Inside were nine boxes of matches

* * *

Now that cautionary cards, long familiar to diabetics, are to be carried by patients who are having long-term anticoagulant therapy, I think it is time that I put into effect an idea which has been in my mind for many years My card or disc, which I shall always wear under my clothes, will read as follows

> I am a doctor If found ill or unconscious do not call in any of the doctors or take me to any of the hospitals whose names are on the reverse side of the disc

It will be such fun having the names engraved.

* * *

We medical students are sometimes more familiar with current theoretical speculations than with current practical treatment in the wards Take tab nihil for example Theoretically nihil is a pure placebo containing nothing except milk sugar, but in the wards it is quite effective therapeutically

Patients complaining of severe headache are given it with the advice " Here is something extra strong for you—just take half a tablet, on no account more!" The next day the doctor asks about the headache and is told that it has completely subsided, the patient has never felt better in his life, he has never had a better treatment, has never met a cleverer doctor

My preliminary investigation of this phenomenon shows that, because of their supposed superpotency, the tablets are in fact rarely if ever taken by the patient He feels a little uneasy about this and, to avoid further trouble with his conscience, tries to persuade the doctor that the tablets had such a splendid effect that no further treatment is necessary My next step is going to be a redouble blind check One group of patients will be given therapeutically active tablets and told they are a placebo, while the controls will get a placebo which they are told is therapeutically active, a second control group will get a placebo which they are told is a placebo Indeed, one of these days I am going to put myself on a course of *normal* saline injections to cure my chain-smoking In our wards normal saline has repeatedly been proved almost as effective as lobeline and it has no side-effects

* * *

In the following correspondence the italics are mine

Dear Dr X, I wonder whether you would admit this patient to your psychiatric rehabilitation centre He is shortly to be discharged from prison after a long sentence for larceny I enclose a copy of his clinical record

Dear Dr Y, Thank you for your letter Although the clinical record of your patient suggests that he is suitable for psychiatric rehabilitation, I regret that we cannot accept him as we only take patients whose behaviour is *antisocial*

Dear Dr X, Thank you for your letter Perhaps you will reconsider your decision when you know more details of the patient's social history He is aged 38 and has served 23 prison sentences, thereby, in his own words, doing " fifteen years' service " His usual practice is to obtain a job *in a hotel*, usually as a kitchen porter He then helps himself to anything he can find He has also in the past been convicted of vagrancy, dangerous driving, being drunk and disorderly, obstructing the police in the course of their duty, causing wilful damage to both public and private property, and of assault Personally I regard him as antisocial I do hope you agree

Dear Dr Y, I regret that I cannot alter my decision about this patient, as we only take patients who are *truly antisocial*

I am hoping to discover whether the words " truly " and " antisocial " have a technical meaning or whether they are psychiatric jargon for full beds

* * *

I once knew a scientist who was prouder of a rejection slip from *Punch* than of all his erudite scientific papers For myself, fame and pride knocked on the door when I became a peripatetic correspondent for the first time. Beside that all my papers on the metabolism of 5, 6, 7-hydroxycholesterol paled into insignificance I was so proud that I showed it to my boss He hasn't spoken to me since I found out later that he became a peripatetic the same day He says he knows the editor I wonder if

* * *

No wonder your correspondent didn't get very far with his one-spur idea I tried it once and the horse went in circles

Letters to the Editor

DEATH OF A BOXER

SIR,—In your issue of April 26 you mention an inquest on a boxer who died after lying in a semicoma for 321 days following a contest

From time immemorial the student of medicine has been taught to look seriously on the most trivial head injury Have his teachers ever made any serious attempt to inform the public how much permanent damage to the brain can and does follow the minor injuries which are normal and inevitable in boxing?

Maudsley Hospital,
London, S E 5

F B BYROM

TREATMENT OF ASTHMA AND HAYFEVER BY HYPNOSIS

SIR,—The importance of clarifying the commonly recognised relationship between psychogenic factors and the clinical manifestations of allergic disorders makes it desirable to submit to critical analysis the report by Dr Mason and Dr Black (April 26) on the abolition of allergic skin-test responses in a patient under treatment of asthma and hayfever by deep hypnosis

They report a progressive loss of skin sensitivity to pollen allergens on the left arm of a patient undergoing weekly hypnosis and skin tests Occasional tests on the left leg, however, continued to give positive reactions, except on one single occasion when the patient was tested on the left leg immediately on waking from a deep hypnotic trance, during which it was suggested to her that there would be no reaction to tests anywhere on the body This loss of skin-test reactivity and the clinical improvement were attributed to the psychogenic effect of the hypnosis

There are, however, alternative explanations for the loss of skin-test reactivity The decreased and then negative reactions on the left arm may have been induced by the repeated vigorous skin testing (10 pricks were made into each site compared with the one prick commonly used for diagnosis) This phenomenon of local loss of sensitivity is not unfamiliar and may be due to local allergic desensitisation to which could be added temporary local loss of skin reactivity due to previous wealing reactions

The inhibition by hypnotic suggestion of a single test on the left leg, performed immediately on waking from a deep hypnotic trance, could be attributed to the well-known modification of peripheral circulation by hypnosis It is a common experience to find that patients who feel even slightly faint during testing, or whose skin is cold, fail to react to skin tests which excite vigorous reactions at other times The wealing responses of the allergic type are acutely dependent upon peripheral blood-flow, which determines the amount of exudation of serum from capillaries rendered permeable by the products of the allergic reaction

The claim by Dr Mason and Dr Black to have produced clinical improvement as well as the skin-test effects by hypnosis may have an alternative explanation

I have had under continued observation for the past 6 years a woman patient nearing 40 years of age who has a long history of severe seasonal asthma On three occasions she has been admitted to hospital in severe status asthmaticus Attempts at "desensitisation" with pollen extracts were marred by reactions due to her extreme degree of hypersensitivity She was instructed to treat herself during the spring and summer of 1956 and 1957 by making a single prick on her arm daily through a drop of 'Pollaccine' (100,000 units per ml) The summers of 1956 and 1957 have been as free of symptoms as the case described by Dr Mason and Dr Black This form of co-seasonal treatment by prick methods is used by many workers to supplement or replace pre-seasonal treatment. Dr Mason and Dr Black's patient could be said to have had such treatment by the vigorous weekly prick tests over a period of 10 weeks

Whilst one would not doubt that psychological treatment may benefit individual patients, the description of individual case-histories can readily be matched, as seen above, from patients treated by either psychological or allergic methods Convincing evidence must in this day and age rest upon carefully controlled trials of adequate numbers of patients A trial of this nature into the specific treatment of pollen asthma by pollen extract injection has shown that more than 80% of pollen asthmatics *derive considerable benefit from this treatment*[1]

Similar well-planned investigations are required for the assessment of psychological methods of treatment in allergic disorders

Tuberculosis Research Unit,
M R C Laboratories,
London, N W 3

J PEPYS

SIR,—It is delightful, and to me at least *not* at all surprising, to get such an excellent and well-controlled *demonstration* (by *Dr Mason and Dr Black* in their paper of April 26) that the workings of the mind and nervous *mechanism* of the body are a necessary factor in the production of hayfever and asthma, and also of the modified and localised forms thereof produced by skin testing with the suitable allergen It is also reassuring to read that this nervous mechanism is only *one* of the necessary factors for their production the Prausnitz transference-of-serum phenomenon remained unaltered

The comparative failure of sedative pills is again satisfactory to the pathologist, for it is a blunderbuss and not a radical treatment They are a great saving of time and trouble for the practitioner, but the patient detects this about as quickly *as he does* and makes the obvious *comments to his* friends

The account of the attempt at desensitisation by injection of pollen extracts is hard to follow on the essential points of dosage, timing, &c, but it sounds as if it has been inadequate

Though the experiments were so satisfying as a demonstration, yet as a routine treatment for, *let us say, 100 chance* hay fever subjects I should think a properly conducted desensitisation course would have the advantage both in producing equally satisfactory results and of causing a *minimal* interference with the daily life of the patient

The personal relationship between patient and doctor is always of the greatest importance, and I suspect *that if* doubts and fears creep into the minds of the *hypnotic* expert and he allows his patients to know of this, *he is* courting failure That is certainly true of a desensitisation course if, at any given point in the course of injections, the practitioner fears a reaction, and by his *demeanour* lets the patient know of this, then reactions he will most assuredly get with all his more suggestible patients The importance of the relationship between patient and doctor is somewhat forgotten *nowadays* by *modern* "medical science"

St Mary's Hospital,
London, W 2

JOHN FREEMAN

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[1] Frankland A W, Augustin, R *Lancet*, 1954, i 1055

GONADAL DYSGENESIS

SIR,—Dr Ferguson-Smith (May 3) is to be congratulated on his enterprise in determining the nuclear sex of 325 male patients in a mental-deficiency hospital He will undoubtedly be followed in his rewarding ætiological foray by a host of chromatographers, endocrinologists, and biochemists He cannot be equally congratulated on his choice of the words "primary microrchidism" to describe his 4 patients with gonadal dysgenesis It is quite true that it is not yet possible to give an exact ætiological description of such cases, but to describe their condition as "microrchidism"—unpronounceable word for the Sassenach—is to relate no more than our grandfathers knew.

The testicular appearances described and the conclusions which Dr Ferguson-Smith draws from his cases have already reached the textbooks [1]

Lawson Wilkins uses the group-term, *gonadal dysgenesis*, and the two types of testicular disorder described by Dr Ferguson-Smith he names "tubular germinal aplasia" and "tubular fibrosis" He recognises that these disorders have a varying pathogenesis The primitive gonad has a *cortex* (germinal epithelium), from which the germ cells are derived, and a *medulla* (mesonephros) from which the tubules and the interstitial cells are developed. He suggests that the defective development of the cortex results in germinal aplasia, while hyaline or fibrotic changes in the tubules may derive either from a defect in development of the medulla or from subsequent regressive changes

We may wait some time for a more exact knowledge of pathogenesis, but we have already a sensible descriptive nomenclature based on rational ætiological ideas

Derby DOUGLAS HUBBLE

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[1] Wilkins, L. The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence p 236, p 265 2nd ed Springfield, Ill

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ATHEROSCLEROSIS AND ITS CEREBRAL COMPLICATIONS IN THE SOUTH AFRICAN BANTU

SIR,—In their stimulating article [2] on this subject, Dr Laurie and Dr Woods make some statements in connection with my findings in atherosclerosis in the Bantu which, in view of the considerable attention this article has attracted, cannot go unchallenged

They state that "In 3000 consecutive necropsies on Bantu in South Africa, Becker (1946) [3] found only 1 cerebral catastrophe, whereas in just under 2000 consecutive necropsies we have found 31 such patients—a prevalence almost fifty times greater than that in Becker's series" This is not correct In my series of 3000 consecutive autopsies, I reported 68 cerebral catastrophes, an overall incidence of 2 3% [4]

The causes of cerebral apoplexy (hæmorrhage and thrombosis) were as follows

	No of cases
Hypertensive arteriosclerosis	33 (*49%*)
Atheromatosis	1 (*1%*)
Congenital aneurysm	7 (*10%*)
Cardiovascular syphilis	2 (*3%*)
Embolism from endocarditis and rheumatic heart-disease	25 (*35%*)

The case ascribed to atheromatosis was one in which it was considered that this condition was the sole cause of the apoplexy; whereas in the cases of hypertensive arteriosclerosis, although atheromatosis was present in 64% of the cases, and in patients over 40 was present in nearly 100%,[3] I considered the hypertensive condition more important in the pathogenesis of the cerebral complication than the atheroma If on the other hand it is assumed, as Laurie and Woods have done, that the major factor in the production of cerebral thrombosis and hæmorrhage is atheromatosis, then the incidence of cerebral catastrophe in my series would rise to about 1% of all necropsy cases, which is comparable with Laurie and Wood's figure of 31 cases in 2000 autopsies (1 5%) In our last 144 consecutive necropsies on Bantu subjects there were 3 cases of cerebral vascular accident (2%)—a small series but perhaps sufficient to show that the incidence of these lesions in the Bantu lies somewhere between 1 and 2%

Laurie and Woods further state that I "found severe atherosclerosis in 26% of Bantu patients over 45, but only in 0 4% of the whole series was atherosclerosis the cause of death" They find a "significant discrepancy" between these two figures which they cannot explain. My definition of severe lesions at that time was "many lesions, together with complications such as dilatation, deformity, calcification, ulceration and thrombosis" I detailed 11 cases in which I considered the cause of death was due solely and entirely to atheromatosis, and clearly stated that it was difficult to assess how far atheroma contributed to the fatal outcome of disease of the cardiovascular system when it was associated with other cardiovascular diseases Of 137 cases which were classed as severe atheroma, 35% died a cardiac death, but many of these cases had evidence of hypertension as well The so-called discrepancy resolves itself into different points of view

Finally, I should like to stress that on occasion the Bantu can and does develop just as much atherosclerosis as the European in this country There is no inherent racial immunity to the disease I believe that the incidence of serious complications in the Bantu, particularly coronary occlusive disease, is significantly lower

Department of Pathology and Microbiology,
University of the Witwatersrand,
Johannesburg B J P BECKER

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[2] Laurie, I M. Woods, J D *Lancet* Feb 1 1958, p 231

[3] Becker B J P *S Afr J med Sci* 1946, 11 97

[4] Becker, B. J P *ibid.* p 1

THE DOCTOR'S ATTITUDE TO HIS PATIENT

SIR,—From the sidelines I have followed this correspondence with growing interest.

My attention was first directed to the subject by Dr Balint's two papers in 1954 [1] and 1955,[2] which whetted my appetite for a careful study of his book.[3] The papers by Dr Clyne [4] and Dr Pasmore [5] were obviously direct results of Dr Balint's teaching and showed that a prophet is not necessarily without honour in his own (or adopted) country

Whilst it would be too much to ask for a universal acceptance of psychoanalytic teaching, it had not seemed to me that Balint, Clyne, Hopkins,[6] and Pasmore had put forward any particularly controversial views they had merely stated facts and observations that any practitioner could confirm for himself if he cared to listen to his patients—though he may have to learn to listen But evidently I was wrong The subject is extremely controversial—and highly charged—and I have no doubt that Dr Balint could give a ready interpretation of the resistances shown

Yet it passes all understanding that anyone should put forward—let alone swallow—the proposition of "Scanner" [7] that "the emotional history should not have any direct influence on the doctor's clinical opinion" That the clinician may reach that opinion "without the emotional history" is no doubt often true; but to say that he "can give just as good advice and get just as good a result without ever hearing it" seems to deny many of the tenets of good medicine, from Hippocrates to Osler and beyond

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[1] Balint, M *Brit med. J* 1954 i, 115

[2] Balint M. *Lancet* 1955, i 684

[3] Balint, M The Doctor, His Patient, and the Illness London, 1957

[4] Clyne, M B *Lancet* Feb 1, 1958, p 232

[5] Pasmore, H. S *ibid* March 8 1958, p 524

[6] Hopkins, P *ibid* 1956, ii 455

[7] *ibid* April 12, 1958, p 800

Having decided that his patient is not suffering from tuberculosis, thyrotoxicosis, or severe heart-disease, but has an anxiety reaction (a not unusual condition) how would "Scanner" proceed with his treatment without ever hearing the emotional history, or could he in fact avoid hearing it? Or would his patient then be left to "recover, remain neurotic or become psychoneurotic"? What is the distinction between neurotic and psychoneurotic?

Dr Clyne's and Dr Pasmore's sails will not be sunk by a damp squib "Scanner" will need a gun of far greater calibre, even though he has Dr Lee [8] and Dr Ryle [9] to play Athos and Porthos to his Aramis

A scanner is presumably one who scans, which though defined as one who looks at closely or scrutinises is also used as meaning one who "glances at quickly, considers hastily" [10]

Nebraska Psychiatric Institute,
Omaha, Nebraska, U S A

FRANK WINSTON

TOXÆMIA OF PREGNANCY

SIR,—My old friend and fellow student Mr Sophian (April 26) and I agree far more than we differ for he has accepted in toto my main thesis, which was regarded as revolutionary when it was first published a quarter of a century ago—that eclampsia results from a disturbance in *la fixité du milieu interieur* He believes that this disturbance is invariably caused by renal cortical ischæmia provoked by a uterorenal reflex

I do not accord the kidneys so exalted a position as he does, for I believe them to be but handmaidens to the hypothalamus and subject to nervous and hormonal control, both direct from the posterior pituitary and indirectly through the anterior pituitary and adrenal glands They must obey to the limits of their structural ability, and are often hampered by mechanical factors The only objection to his simple theoretical schema is that it does not work in practice, for hypertension, proteinuria, and œdema can occur independently of each other and in different sequences, while eclampsia occurs apart from any of these three signs

I very much appreciate Mr Sophian's generous remarks about my operation for denervating the internal iliac vessels As he knows, I have been interested in the effects of afferent nervous stimuli on renal secretion since 1934 [11] and agree with him that impulses from the uterus can affect the secretion of urine, cause pallor, sweating, vomiting, a profound fall in blood-pressure, bradycardia, and acute dilatation of the pupils, and initiate the onset of labour I merely feel that there is no justification for postulating a unique uterorenal reflex when similar effects on the kidney can be caused by afferent stimuli from other parts of the body

I wonder whether Mr Sophian would be so very kind as to give direct answers to the following three questions

(1) Infants, non-pregnant women, and men die from renal cortical necrosis If toxæmia of pregnancy results from cortical ischæmia why is eclampsia peculiar to the pregnant state?

(2) If resistance to uterine stretch is the stimulus which provokes renal ischæmia how is it that bilateral renal cortical necrosis practically never occurs in primigravidæ but is most likely to occur in association with toxæmic accidental hæmorrhage in a single pregnancy at about the seventh month in a woman who has previously borne 4 or more full-term children without toxæmic symptoms?

(3) How is it that patients with true eclampsia may secrete urine freely?

"Algebraic pebbles" together with the cooperation of the local health authorities, general practitioners, and hospital staff have reduced the incidence of eclampsia in Bradford, from 3 8 to 0 2 per 1000, and the number of cases of hypertension plus proteinuria by half, over a period of ten years The Medical Research Council have advised the Government that in their view there is a strong probability that cigarette smoking provokes carcinoma of the lung I submit that these figures from Bradford together with those from Siam, Hong Kong, Ceylon, and the Fiji Islands, provide a much stronger case for the thesis that eclampsia is to be attributed to imperfect nutrition together with the disadvantageous mechanical factors associated with pregnancy and the upright position

Bradford

G W THEOBALD

INFANTILE GASTROENTERITIS

SIR,—I am afraid Dr Sangster (April 26) has again begged the question of the essential place of *Escherichia coli* in this disease

All the references (1–5) he gives relate to work prior to 1948, when *Esch coli neapolitanum* was isolated by Bray Apart from serotyping, I have yet to see any new fundamental work stemming from this time

Cow's milk cannot be the whole answer, for the disease occurs in breast-fed infants as well, especially in maternity units

It is true that intestinal organisms enter by the mouth, but bottle-fed and breast-fed infants do not feed themselves or prepare their food The question of adult human carriers is surely, therefore, of paramount importance

I cannot accept that with present-day techniques the problem of isolating a virus, if any, is insuperable The question of serotyping is merely a refinement which does not invalidate the initial premise

Even the eminent source of the Royal College of Physicians of Edinburgh publication, to which Dr Sangster referred, failed to produce any adequate evidence to enlighten our essential ignorance of this intriguing condition

Ilford Isolation Hospital,
Chadwell Heath, Romford, Essex

I M LIBRACH

EFFECT OF HEAT ON SPASTICITY OF DISSEMINATED SCLEROSIS

SIR,—I read with great interest Dr Lyburn's letter of March 15 I agree with him that in multiple sclerosis the weakness and spasticity are greater in warm weather, and that the patients feel better when it is cool—a mild spring or autumn being their best time This is in keeping with the fact that excessive movement or massage or permanent confinement to bed is bad for these patients

Thrombi in the small veins of the central nervous system may be found, according to my observations, in as many as 90% of cases But I believe they should be regarded as a manifestation of an allergic process My histological findings in 20 cases of multiple sclerosis [1] seem to correspond fully with the well-known histological picture of neuroallergy as induced in animals or found in man

(1) hyaline degeneration and fibrous "delamination" of the vascular wall, (2) œdema and swelling of the endothelial cells,

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[8] Lee, B *ibid* p 801
[9] Ryle A *ibid*
[10] Webster's New World Dictionary New York 1957
[11] Theobald G W *J Physiol* 1934, 81, 243 The Pregnancy Toxæmias, p 370, London 1955

[1] Lehoczky, T Neuroallergischen Beziehungen in der Histopathologie der multiplen Sklerose Published by Hungarian Academy of Medicine Budapest, 1957

(3) precapillary and capillary dilatation, prestasis, and stasis, (4), capillary and precapillary thrombosis, (5) perivascular infiltration, (6) hæmorrhage, (7) perivascular, perifocal, and diffuse tissue œdema, (8) partial and total necrosis, (9) perivascular parenchyma rarefaction, (10) granuloma formation, and activity of the microglia cells and histiocytes

These histological changes extend over the whole central nervous system that is to say, they can be found in parts of the brain or spinal tissue which do not contain plaques This too is strong evidence of an allergic origin.

Istvan Hospital,
Budapest

T LEHOCZKY.

UNILATERAL RENAL INJURY DUE TO TRANSLUMBAR AORTOGRAPHY

SIR,—The conclusion drawn in Mr Clark's article (April 12) merits further consideration

A large quantity of dye was injected, using a mechanical pressure apparatus, directly into the right renal artery In a recent survey McAfee[1] concluded that the risk of injury to the kidneys depends on the amount of contrast medium reaching them, the instance of complications being trebled if more than 40 ml of dye was used. The risk of renal damage cannot be entirely eliminated but can be considerably reduced if no more than 25 ml of contrast medium is manually injected after a small pilot injection is made to localise the needle site with reference to the renal artery

The new contrast media 'Urografin' and 'Hypaque' may prove less toxic than 'Diaginol' Furthermore, Mr Clark gives no evidence to show that the right kidney functioned normally before aortography, urine analysis after the examination showed no abnormal constituents which may have been expected if renal damage had occurred during the examination.

Department of Radiology
United Liverpool Hospitals
Liverpool

AUDREY COUCH
RAYMOND W GALLOWAY

CIGARETTE-SMOKING AND DISEASE

SIR,—The rising mortality from lung cancer and coronary thrombosis in older men is rightly described as a smudge on the picture of health in Scotland (April 12, p 789) Need one look far for the responsible "morbid process"? Surely not there is enough evidence for a prima-facie case against cigarette-smoking This addiction is probably also a big factor in Scotland's high morbidity (and mortality) rate from bronchitis

This report from Scotland should re-emphasise the great need for adequate anti-smoking education. Lung cancer (only one of the lethal complications of smoking) is killing nearly four times as many people as tuberculosis, but there is no corresponding official campaign of prevention. On the contrary, the barrage of tobacco advertising is permitted to continue unchecked, even when it is clearly aimed at adolescents Political fears about loss of revenue from tobacco taxation are always being emphasised, but what of the decimation of the male smoking population, what of the dollars spent on tobacco, and what of the fires and pit accidents caused by smokers? There are two views to be taken of the financial situation, and Dr Hugh Dalton did well to remind the House of Commons of this last week.

But there is only one reasonable view of the medical situation and it is high time the public was bluntly and decisively warned of the dangers There has been too much medical circumlocution already the use of such terms as "an association", "a link", "a connection", and even "a cause-and-effect relationship" between cigarette-smoking and lung cancer is too vague The public still thinks there is some reasonable doubt about it all. There is not, of course, and we should be honest and say "Most cases of lung cancer are the result of years of cigarette-smoking"

Dr Beynon (April 12, p 795) could do a considerable service by advising all *smokers* over 35 years of age in his area to have a twice-yearly chest radiograph Directly, he would find early cases of lung cancer, indirectly, he would educate the public in one of the dangers of this expensive and harmful form of self-indulgence He might even provide Mr Stocker (April 12, p 797) with some valuable experimental information

Leicester

J P ANDERSON

THIRST

SIR,—Your annotation on thirst (April 19) seems to confuse measurement of true osmotic values across semi-permeable membranes with an estimate of it obtained indirectly by determining the concentration of solute particles in a solvent—e g, by estimating freezing-point depression

Where a solution contains both diffusible and non-diffusible particles these two methods are bound to give different results Since we have this condition in biological materials, measurement of freezing-point depression is not a valid method for determining osmotic-pressure differences unless allowance can be made for the concentration of diffusible particles Since urea is believed to be distributed freely through total-body-water it cannot produce an osmotic gradient within the body If the cells of a "thirst centre" respond to changes in osmotic pressure they could not be expected to be influenced by changes in concentration of urea

The exceedingly complex permeability of cell membranes to different molecules and ions makes measurement of the real osmotic gradient in biological material very difficult Since we cannot readily produce artificial membranes whose permeabilities correspond to those of cell membranes and since the indirect methods of measuring osmotic pressure by freezing point depression and boiling-point elevation are not valid, one has usually to be content with a very crude reproduction of the cell membrane and with measurement of the osmotic gradient across it Perusal of the literature on osmotic pressure of biological systems makes it obvious that much confusion of thought exists and too often the writers fail to distinguish between the osmotic gradient and the value of the total osmotic pressure based on a method which really measures total concentration of solute particles

I am also rather astonished that your annotation should state that pure salt depletion can give rise to a sensation of thirst. It is usually considered that thirst is minimal or absent in pure salt depletion

Glasgow Royal Infirmary

JAS C EATON

⁂ Dr Eaton is referring to the difference between, on the one hand, the osmotic pressure of a solution, which, like the freezing-point and the vapour pressure, depends on the concentration of solute particles, and, on the other hand, the "effective" osmotic pressure, representing the osmotic gradient across the cell membrane

It seems very doubtful whether an osmotic gradient is maintained across all membranes a difference of osmotic pressure is probably rapidly abolished by a movement of water across the membrane.

The different effects of urea and sodium are probably to be explained by the different permeability of cell membranes to these substances, an increase in the concentration of urea does not affect the water content of cells, but an increase in the concentration of sodium (limited to the extracellular fluid) causes the cells to shrink.

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[1] McAfee, J G *Radiology* 1957, 68, 825

While it seems paradoxical that sodium deficiency should produce thirst, it nevertheless seems to do so,[1,2] if thirst is defined as a desire for water —Ed L

NEW METHOD OF PHENOBARBITONE ADMINISTRATION

Sir,—I find it difficult to understand the letters written by Dr Pearson (April 19) and Dr Penman (March 29) Dr Penman states in his opening sentence that "no conclusion whatever can be drawn from the data presented by Dr O'Connor last week" Dr Pearson writes that "I cannot agree that Dr O'Connor has really demonstrated anything"

It appears to me that Dr O'Connor has demonstrated that when he treated 18 cases of epilepsy with the long-acting phenobarbitone 'Spansules', he virtually cured all the patients he treated On re-reading Dr O'Connor's article, I agree that it is open to criticism in many ways Nevertheless, if we are to believe what he has written, he has shown that with this long-acting phenobarbitone therapy a method has been suggested which may be of great value in the treatment of epilepsy His work may have been uncontrolled, but he has still demonstrated, even if only as a clinical observation, that all the cases he treated improved to such an extent that the results are really striking These results surely should not be ignored, even though he cannot explain them satisfactorily Dr O'Connor has produced enough evidence to stimulate a trial of delayed-absorption phenobarbitone in epilepsy by others

London, N W 3 H N Levitt

INDIRECT BILIRUBINÆMIA

Sir,—In your issue of April 19, Dr Schmid and his colleagues comment on our recent report dealing with the reduction of indirect bilirubinæmia They state that they have not been able to duplicate our results, they suggest that we may be doing harm by driving bilirubin from the blood to the tissues, increasing the risk of brain damage, and they urge all to desist from this therapy until further pharmacodynamic studies of glucuronic acid are carried out

It goes without saying that all new drugs should be thoroughly tested before clinical use and that they should not be used without due information in regard to their pharmacodynamic action We might point out, however, that glucuronic acid, although not previously used for this particular purpose, is by no means a new drug It has been known for two generations and its safe and toxic levels are documented [3] There are numerous references dealing with its administration to experimental animals and to man

Our critics do not document the basis of their expressed fear that by lowering the blood-bilirubin we are driving it into the tissues We have not, to be sure, taken biopsies of the brain before and after glucuronic-acid therapy, but we have observed a diminution of jaundice and biopsies of the subcutaneous fat have shown a reduction in indirect bilirubin coincident with the fall in blood levels

It would seem that the discrepancy between the results of the Boston workers and our own may be explained by differences in technique This matter is now being explored It would seem to us unfortunate if the concern of our Boston colleagues were to result in discontinuance of further studies with this promising therapeutic approach

Stuart Danoff
Charlotte Grantz
Audrey Boyer
New York University College of Medicine L Emmett Holt, jr

THE ROYAL COMMISSION AND RESTORATION OF GENERAL PRACTICE

Sir,—Lord Moran, in his evidence to the Royal Commission in January, pictured a professional ladder, consultants on the rungs and general practitioners at its foot, pay corresponding A little later, in *The Lancet* (Jan 25, p 216), he wrote of "the very high standard of general practice as he had known it" That the family doctor is not "what he used to be", coming from a leading medical authority and at a time of reduced public esteem, amounts to a professional calamity The following brief study serves to show that there is sufficient underlying cause for impaired service in the bad conditions of work in general practice Until these defects are remedied by the Ministry of Health it is imprudent to impugn the professional ability of the doctors

During the strain of war, the work of general practitioners was a decisive factor in maintaining national physique and morale Doctors are due to share in the benefits of victory, but the Government leaves them with antiquated machinery to carry on, as best they can, waging their unceasing war against disease and suffering in the community To strike for better conditions is, naturally, rather repugnant to them as it would cause some interruption in the treatment of their patients

Conditions in General Practice

The inherent difficulties of day-to-day practice are daunting enough The doctor's patients are "on his doorstep" or have to be visited in the vicinity Calls come any time, day or night, and epidemics upset his routine and deprive him of his rest Whatever the ailment, it has to be diagnosed, the patient satisfied and anxious relatives coped with Such duties call for all the virtues, a wearing business A haggling and cheese paring attitude on the part of the Government towards them is likely to intensify the present grievance of general practitioners

The bad conditions in practice have persisted since the 1948 Act owing to the complacency of the authorities They involve patients in avoidable suffering and act as a damper on professional zeal and enterprise Among glaring examples is the permission of too high a maximum number of patients This danger is all the greater when modern aids to effective treatment go unprovided These ancillaries should at least equal standards current in commerce Technical and secretarial assistance as well as up-to-date equipment are wanted *Time* for due deliberation is an indispensable ingredient of successful clinical work, and this truth is endorsed by Sir Hugh Watson speaking at and as a member of the Commission [1] when he said, "Assuming that they have the time to do it?" These words reveal a layman's uneasiness about the harassed doctor

Finally, to gain its ideal objective, the cultivation of a healthy nation, not merely to alleviate disease, the Ministry needs to recognise that general practice is the proper and effective agency Only the family doctor has access to the intimacies of family life and his instruction on simple principles of the care of the body will be acceptable to parents The population is now sufficiently educated to cooperate If the Ministry will include this provision in their functions, it will at last be justified in calling itself a *National Health* service The cost will be repaid by the gradual elimination of the huge expenditure on sickness benefits and on drugs at present required owing to ignorant abuse of the human body

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[1] Cizek, L J, Semple, R E, Huang, K C, Gregersen, M I *Amer J Physiol* 1951, 164, 415

[2] Strauss M B *Arch intern Med* 1958, 101, 216

[3] Artz N E, Osman, E M Biochemistry of Glucuronic Acid New York, 1950

[1] *Brit med J* Jan 25, 1958, suppl p 31

Consultant Conditions

This calls for attention, as it proves, by sharp contrast, that the Ministry is quite capable of bettering conditions in the National Health Service

Consultants spend most of their time in hospitals and, there, great facilities have been added since 1948 Notable is the increased number and range of service of registrars Further, thanks to a whole host of ancillaries, professional, technical, and clerical, the consultant can increasingly concentrate on his expert duties Costly complex equipment, too, has been freely supplied The consultants are now paid for hospital services as well as continuing to enjoy the fruits of private practice which have persisted in substantial measure

Consultants are well paid and generously equipped with the means of up-to-date service Family doctors fare badly in both respects It is not the occasion for discrediting their skill, but rather to commend their steadfast adherence to their exacting duties carried on despite the scant attention to the remedy of bad conditions It is said that bad workmen complain of their tools, but good workmen won't work with bad ones The doctor, however, has to do so indefinitely and this although the health of Britain is at stake

A successful outcome of the work of the Commission depends on radical upgrading of conditions in general practice, not merely relieving the present uneasy situation regarding remuneration

Bristol A WILFRID ADAMS

INTERMITTENT HYPERPARATHYROIDISM

SIR,—My interest in the paper by Dr. Whitby (April 26) prompts me to stress a few points As far as I know, only scanty data are available concerning the renal output of calcium in normal persons But according to my knowledge and own experience, I should consider the urinary calcium output of 265 mg per 24 hours on an ordinary diet and 150 mg on a daily intake of 120 mg as distinctly abnormal What is important, however, is to follow the calcium output daily and if possible even in a normal control from the same ward and on the same diet. One would then feel more confident about the interpretation of the results

An early diagnosis of hyperparathyroidism is possible only from a study of the calcium output in the urine First, when renal function is reduced by calcium deposits, there will be a rise of serum-calcium There is every reason to believe that hyperparathyroidism in its earliest stage cannot be diagnosed or excluded by serum-calcium determination alone The data presented by Dr Whitby evidently show that the correct diagnosis has been made at an earlier stage than usual But I still consider his case to have been non-intermittent. More extended data would probably have shown this

St Joseph s Hospital,
Porsgrunn, Norway A SCHRUMPF

THE FUTURE OF THE PUBLIC HEALTH LABORATORY SERVICE

SIR,—As a bacteriologist in the National Health Service I should like to confirm, from my own experience, the criticisms of the conditions of work which are made by "London Bacteriologist" in his letter of April 26

The masquerade as general pathologist which he mentions can be irritating, but the interference with bacteriological work by pathologists-in-charge, particularly of the know-it-all-clinical-pathologist type, is the more serious matter

"Provincial Pathologist" in his letter of April 12 advocates a closer integration of the Public Health Laboratory Service with the hospital services In case anything of the kind does happen in the future, it seems fair to offer to one's bacteriologist colleagues, who may face "integration," a word in season

HOSPITAL BACTERIOLOGIST

EFFECT OF RELAXIN ON UTERINE MOTILITY IN VITRO FOLLOWING TREATMENT WITH ŒSTRADIOL AND PROGESTERONE

SIR,—The effect of relaxin on the tissues thought to constitute the target organs for this substance presupposes pretreatment of the animal with œstrogenic hormones It has been possible to demonstrate this interaction of œstradiol and relaxin both through the biochemical changes induced in the myometrium by these hormonal substances and through the contraction-inhibiting effect of relaxin on the uterus [1] Steinetz et al [2] have shown that the hormonal balance between relaxin and progesterone affects the course of delivery in mice

The reciprocal action between the lipid-soluble ovarian hormones and relaxin may be of decisive importance for an understanding of the significance of relaxin for uterine motility

The aim of the present investigation has been to study the effect of relaxin upon uterine motility in vitro as influenced by these steroid hormones

The animals used in the experiments were virgin female rats (weight 200–250 g) and mice (weight 18–22 g) The animals were castrated 14 days before starting the injections of the respective steroid hormones (Œstradiol benzoate ['Ovex B,' Leo] 1 µg in 0·05 ml peanut oil Progesterone ['Progestin,' Pharmacia] 1 mg in 0 08 ml peanut oil) The injections were given subcutaneously for 3 days (2 µg œstradiol and/or 2–2 5 mg progesterone to the rats, and 1 µg œstradiol and/or 2 mg progesterone to the mice in alternating combinations) The relaxin preparations used were firstly an extract with a biological activity corresponding to about 150 guineapig units per mg and secondly an extract prepared from pregnant sow ovaries by the method of Frieden and Hisaw [3] The animals were killed on the 4th day by a blow on the head The test method with in-vitro experiments has been described earlier [4]

Castrated animals —The motility pattern of the curves had a typical appearance, with high frequency and low amplitude Relaxin did not affect the contractions even in relatively large doses (up to 100 µg , larger doses were not tried)

Animals treated with œstradiol —Obvious reduction or cessation of the activity with relaxin doses down to 1–2 µg There was only slight, if any, impairment of tone

Animals treated with progesterone (these experiments were carried out on rats only) —Relaxin did not affect the spontaneous activity With 500 µg , however, there was slight impairment of tone

Animals treated with œstradiol and progesterone —The spontaneous contractions of the rat uterus were generally reduced in amplitude by relaxin even in very small doses down to 2 µg In contradistinction to the results after treatment with œstradiol alone, tone was obviously impaired The corresponding curves from mice showed the motility to be affected to only a minor degree, whereas an impairment of tone was clearly apparent in all experiments Both the spontaneous activity and the tone impairment were reversible if the doses of relaxin were not too large.

In-vitro experiments after injection of relaxin in vivo —In a number of experiments mice were treated with œstradiol or œstradiol-progesterone with the same doses as previously On the 4th day, 3–4 hours before they were killed, the animals were given injections of relaxin in doses varying between 0 8 and 10 mg subcutaneously in saline solution or 20% polyvidone

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1 Miller, J W , Kiseley, A , Murray, W J *J Pharmacol* 1957, 120, 426
2 Steinetz, B G , Beach, V L , Kroc, R. L *Endocrinology*, 1957, 61, 271
3 Frieden, E H , Hisaw, F L *Arch Biochem* 1950, 29, 166
4 Wiqvist, N , Paul, K.-G *Acta endocr , Copenhagen* (in the press)

On the assumption that the increase in the water and glycogen content of the myometrium seen in rats 3–6 hours after the injection of relaxin also occurs in mice, one might within this interval expect that in subsequent in-vitro experiments the uterus would not show any spontaneous activity However, in all cases the uterus manifested lively spontaneous activity On the injection of relaxin in vitro there was in animals treated with œstradiol-progesterone no impairment of either the motility or the tone (relaxin doses of up to 100 µg , larger doses were not tried) In the œstradiol-treated animals the uterus reacted relatively weakly in a few experiments and in most cases practically not at all Tone remained unaffected

The results show that, with the doses used, relaxin affects the uterus only when the animals have been pretreated with œstradiol This has been shown previously by Miller et al [1] In this respect œstradiol cannot be replaced by, progesterone as a relaxin-sensitising steroid hormone

After pretreatment of the animals with œstradiol and progesterone, there is striking impairment of tone as well as varying reduction of motility Krantz et al [5] say that the intravenous injection of relaxin in virgin œstradiol-treated guineapigs " invariably resulted in diminution of tone and spontaneous uterine motility " Apart from this, I have not been able to find any data concerning the effect of relaxin on uterine tone

3 hours after a large dose of relaxin injected in vivo the uterus still showed lively spontaneous motility in vitro The time for the maximum effect on the myometrium of the biochemical and physical changes thus does not coincide with the maximum effect upon the motility On the other hand, under these circumstances the uterus is refractory to the direct administration of relaxin in vitro as regards changes in tone and motility As an interesting parallel to this one may mention the effect [6 7] of relaxin upon the uterine motility in women Relaxin had its most pronounced effect during the proliferative phase, a lesser effect during the phase of secretion, and a very inconsiderable effect in the course of labour This may be because endogenous relaxin, especially during pregnancy and possibly also during the phase of secretion, has desensitised the myometrium to exogenous relaxin

Department of Women's Diseases,
Karolinska Sjukhuset,
Stockholm

Nils Wiqvist

The first relaxin extract was kindly supplied by Dr R L Kroc, Warner-Chilcott Laboratories, and the second by Dr K-G Paul, Medical Nobel Institute, Stockholm

PURPURIC ERUPTION DUE TO CARBROMAL

Sir,—More cases of drug rash due to carbromal seem to be about

Carbromal is a capillary-damaging agent, but a relatively weak one, so the purpuric component tends to be unobtrusive and the diagnosis is sometimes missed The eruption, however, which has been fully described by Borrie,[8] is very constant in pattern and distribution It appears first on the ankles and spreads slowly up the lower limbs to the buttocks and hips, later involving, if the drug is not withdrawn, the forearms and other parts There are reddish-brown patches covered generally with fine scales on a background of tiny petechial spots and faint reticulated pigmentation Itching is variable

Carbromal has been regarded as innocuous and can be obtained without a doctor's prescription Apart from tabs carbromal *B P C* it is contained in various proprietary sedative and sleeping tablets, such as ' Abasin ', ' Adalin ', ' Carbrital ', ' Dormiprin ', ' Dormupax ', ' Persomnia ', ' Noctynol ', ' Relaxa ', ' Sedaltine ', and ' Somnotil ' Some compound remedies also contain carbromal, when their trade names and principal therapeutic purpose may not lead one to suspect its presence. For instance, a patient recently presented with what appeared to be a characteristic carbromal eruption, but I was puzzled because she had not been taking ' Persomnia ' or other sleeping pills that I knew contained carbromal She had, however, for many months been having ' Hyperysin ' (anti-hypertensive and vasodilator), which I later discovered has a carbromal content of gr 3 per tablet This led me for future reference to look up the formulæ of other proprietary preparations and I found a carbromal content, surprisingly, in ' Viredrin ' (compound male hormone tablets), ' Fydalex ' (antispasmodic), ' Menopax Oral ' (œstrogenic compound) and ' Menovo ' There may be others

London, W 1

E W Prosser Thomas

VISITING PARENTS IN HOSPITAL

Sir,—Now that there is widespread agreement that children in hospital should be visited daily by their parents, may I put in a plea for the visiting of ill parents in adult hospitals by their children ?

Department of Child Health,
University of Sheffield

R S Illingworth

AN UNUSUAL INJURY

Sir,—The following injury seems sufficiently unusual to make it worth recording

A man, aged 52, was employed as a press operator in charge of an electrically-operated machine making plastic parts by an injection moulding process The plastic material in the moulding machine was kept at about 450°F (176°C) to keep it sufficiently fluid to enter *all* parts of the die *At one stage in the* process the operator of the machine has to remove the moulded product by putting his hand between the separated valves of the die and, in so doing, across the aperture of the injection nozzle Safety devices normally ensure that no part of the process, which is almost entirely automatic, can take place while the die valves are separated and the safety gate open

On the occasion of the injury, the operator had the back of his right wrist opposite the injection nozzle when, for a reason that has baffled the makers of the machine, he suddenly received a forcible injection of semi-solid polystyrene into the back of his wrist

When admitted to the casualty department shortly afterwards, he was seen to have a knob of solid plastic material, about the size of a pigeon's egg, projecting from the dorsum of his wrist slightly above a line joining the ulna and radial styloid processes It gave the appearance of the end of a bullet-shaped mass A radiograph showed a fracture of the distal end of the ulna without displacement, but the object, which was not radio-opaque, could not be made out

Under a brachial-plexus block an attempt to remove the object by direct pulling was unsuccessful, so an incision was made on either side of the entry hole in the line of the forearm It was then seen that the plastic material had mushroomed out under the subcutaneous tissues, having met the deeper structures overlying the end of the radius, and had also fractured the end of the ulna

The photograph of the specimen shows above, the knob that was projecting from the small entry hole, the central

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5 Krantz, J C , Bryant, H H , Carr, C J *Surg Gynec Obstet* 1950, 90, 372
6 Posse N , Kelly, J *ibid* 1956, 103, 687
7 Kelly, J Posse, N *Obstet Gynec* 1956, 8, 531
8 Borrie, P *Brit med J* 1955, i, 645

mushroomed portion grooved on one side by one of the extensor tendons, and, below, the spur which had entered the fracture site in the ulna. The object was shelled out without much difficulty, and, although the subcutaneous tissues were only doubtfully viable owing to the initially high temperature of the plastic, primary closure was attempted. The wrist and forearm were then put in plaster-of-paris splint.

The superficial tissue over the head of the ulna later sloughed, and the defect was covered by Thiersch grafting. There was some residual stiffness of the wrist, but the patient was able to resume work four months after his injury.

I am very grateful to Mr. J. B. Scott for permission to report this case and for his details of the subsequent course of the patient, and to the photographic department of the Royal Berkshire Hospital for preparing the photograph, and the patient's employers for showing me the machinery and technical details related to the accident.

London School of Hygiene and Tropical Medicine,
London, W.C.1
E. R. NYE

Parliament

Supplies of Poliomyelitis Vaccine

ON May 1 Dr. EDITH SUMMERSKILL criticised the Minister of Health for his failure to ensure that adequate supplies of the vaccine were available to carry out even the modest scheme of immunisation which this country was offering. We were, she pointed out, only offering to immunise children from 2 to 15 years of age and expectant mothers, while other countries were offering to immunise all people under 40, and we must remember that two-thirds of the deaths from poliomyelitis occurred among adults not children. While we were offering two injections, in Canada and the United States three were given. She also thought that the Ministry had not publicised the campaign sufficiently. As a result only 40% of the 10 million eligible had registered by the end of February. The choice of vaccine offered—British or Salk—tended to sow seeds of distrust in the minds of ordinary people. The latest figures, at the end of February, showed that of those registered 571,000 had been given one injection and 2,688,000 were still waiting for the first injection. Thousands more were estimated to have registered in March and April. The initial arrangement to buy vaccine from the United States was not made till September, 1957, and the vaccine took six months to produce and test. She considered that the Minister had failed to order sufficient supplies from the United States soon enough. Delays in the preparation of the vaccine had occurred, both here and in America, but these hazards should have been expected.

Mr. DEREK WALKER-SMITH, the Minister of Health, said that the original order for 5000 litres of Salk vaccine was made in September, 1957, as a bridging operation until British supplies should be available. His expert advice had been then, and still was, that British vaccine, when available, was the best and constituted the best long-term basis for our use. At that time, there was every reasonable expectation that 1958 would see mounting supplies of the British vaccine from at least two large and independent sources. Nobody could have foreseen that British production would be almost at a standstill for several months in 1958. To remedy the lack of British vaccine, 2800 litres of Salk were ordered in January, subject to check testing, with the expectation that they would emerge from the tests, if successful, in the course of April and May. These should have been our main source of supply for the present period. But the American and Canadian suppliers had also met difficulties, which with the almost total postponement of British supplies, had caused a major set-back to our programme. In this emergency the Government had asked the Medical Research Council whether, in view of the shortfall of supplies, American and Canadian Salk vaccine which had passed safety tests in the country of origin could be used in this country without further tests. After considering the present situation the M.R.C. had agreed to this as a temporary measure.[1] A million doses of vaccine, part British, part Canadian, had been issued in the last two weeks, and substantial new supplies would now follow hotfoot and would meet the full requirements of the local authorities, not only for those who had already registered but also for those who would register in the coming weeks and months.

The M.R.C., he continued, had advised this relaxation as a temporary measure, and he wanted to make it clear that this opinion in no way derogated from its general view that British vaccine was best, and that in general the greater the sizes and number of samples tested the better. The Government proposed to restore check testing by the M.R.C. at the earliest possible moment, and looked forward to the possibility that one day we could dispense with the need to use any vaccine containing the Mahoney strain, but this day was not yet, because of the present uncertainty surrounding the British supply position. Meanwhile they would proceed with the work in hand on the basis of the M.R.C.'s immediate advice. There still was a right to reject the Salk vaccine if people preferred to wait for the British vaccine. This was logical, since there was, in any event, no obligation on anybody to register for vaccination at all. People would still have this right of refusal if they prefer to wait, either for the British vaccine or for Salk vaccine check tested by the M.R.C. This was a decision which the individual might find hard. But he could take his doctor's advice.

N.H.S. Contributions

THE National Health Service Contributions Act, 1958, received the royal assent on April 30.

QUESTION TIME

Working Party on Hospital Staffing

Dr. DICKSON MABON asked the Secretary of State for Scotland if he would make a statement on his discussions with the Scottish Joint Consultants' Committee.—Mr. JOHN MACLAY replied: It has been agreed that the study of hospital staffing structure will be conducted on a Great Britain basis, and that interim arrangements for senior registrars will be made, the actual arrangements are to be discussed at a further meeting.

Mr. KENNETH ROBINSON asked the Minister of Health if he would widen the membership of the proposed working party on the medical staffing structure of the hospitals to include representatives of bodies other than the Joint Consultants' Committee and his department.—Mr. DEREK WALKER-SMITH replied: I would refer to the answer given by the Secretary of State for Scotland. My right hon. Friend and I are not proposing any change for our part. Mr. ROBINSON: Is the Minister aware that there are those in the profession who believe that the advice he will receive from the Joint Consultants' Committee may not be entirely detached? Does he not think there is at least a case for having one representative of the senior registrars on the working party?—Mr. WALKER-SMITH: This is a joint committee of my right hon. Friend and myself and the Joint Consultants' Committee in cooperation. The Joint Committee consists of representatives of the Royal Colleges, the Scottish Royal Corporations and the British Medical Association. Its composition is a matter for these three bodies, and my right hon. Friend and I cannot interfere with the professional representation on this working party, which is a matter for the profession. Mr. ROBINSON: Is the Minister not aware that those people are all consultants? As well as representatives from the right hon. Gentleman's department and the Joint Consultants' Committee, could not the Minister include one or more representatives of the senior registrars?—Mr. WALKER-SMITH: The composition of the membership of the working party is not yet decided. We shall have to appoint our members, and I will bear in mind what the hon. Member has said. I cannot, however, interfere with the professional representation, which is a matter for the profession.

Mr. ROBINSON asked the Minister if he would instruct the working party on the medical staffing structure of the hospitals to pay special attention to the understaffing of the mental hospitals and to the need for a substantial increase in the number of psychiatrists in all grades —Mr **WALKER-SMITH** replied The terms of reference of the working party apply equally to mental and other hospitals and no specific reference seems necessary Mr **ROBINSON** In view of the fact that this is by far the most undermanned specialty in the whole of the hospital service, does the Minister not think that at least one word on this problem might be included in the terms of reference?—Mr **WALKER-SMITH** The hon Member can take it that a joint body such as this will be fully aware of all the circumstances relating to the structure and staffing of the mental and mental-deficiency hospitals

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[1] The Council's memorandum on this subject appears on p. 1016.

Amenity Beds

Mr **JOHN HALL** asked *the Minister if he would abolish* hospital private beds and replace them by the same or greater number of amenity beds —Mr **WALKER-SMITH** replied No, Sir

Mr **HALL** Is the Minister aware that the demand for these amenity beds by those to whom privacy is essential for speedy recovery is far greater than the number available? As a result, they are being forced into private beds at a very great and sometimes extortionate cost? Will he reconsider his decision? —Mr **WALKER-SMITH** I am always prepared to consider proposals both for private or amenity beds where this is possible and where, in the view of the regional hospital board, there is a demand, but there is still a demand for private treatment, and I do not think it would be appropriate to go back on the decision which the House took in this regard in 1946

Russian Vaccine for Multiple Sclerosis

Mr **FENNER BROCKWAY** asked the Minister what information he now had as to the efficacy of the Russian vaccine for multiple sclerosis —Mr **WALKER-SMITH** replied I cannot as yet add to the replies [1] I gave to questions on this subject on April 21 and 28

Mr **SOMERVILLE HASTINGS** asked the Minister if, after having received the information from Russia that he was now seeking, he would issue a white-paper so that both doctors and the public would have reliable information available —Mr **WALKER-SMITH** *replied I do not think this course would be* appropriate since the responsibility for using the vaccine must rest with the doctor, not the patient I will continue to ensure that any information reaching me is made available to doctors who wish to use the vaccine Mr **HASTINGS** Could the Minister arrange at frequent intervals that the latest information which he has to hand is provided for the medical profession through his Ministry or through one of the journals, or in any other way he thinks to be appropriate? Mr **WALKER-SMITH** The ordinary method of communicating information to the medical profession is through the medical Press, supplemented, if necessary, in the case of those practising in the National Health Service, by references in *Prescribers' Notes* I will certainly bear all those matters in mind

Dr **EDITH SUMMERSKILL** Is it not almost unprecedented for a Minister of Health to pass on to doctors information about a vaccine from a foreign country while at the same time he refuses to undertake any tests of the vaccine?—Mr **WALKER-SMITH** What the hon Gentleman asked me to do was to make available in a suitable form to the medical profession such information as we have I must say that I thought that was a very reasonable request, which I said I would try to meet.

Persomnia

Mr **JOHN RANKIN** asked the Minister what had been the outcome of his consultations with the Secretary of State for the Home Department about the sale of 'Persomnia' without prescription from a registered medical practitioner —Mr **WALKER-SMITH** The matter has been referred to the Poisons Board Mr **RANKIN** Without seeking to rush matters in any way, may I ask the Minister whether he has any idea when the Board will report?—Mr **WALKER-SMITH** I have no precise indication The Board is an independent statutory body advising the Home Secretary on these matters, and I have no doubt that it is proceeding with the greatest speed which is compatible with thoroughness and efficiency Mrs **HARRIET SLATER** Is not the Minister aware that the Poisons Board was asked to look at the matter some eighteen months ago?—Mr **WALKER-SMITH** I recognise the hon Lady's interest in this matter over a period, but I am sure she agrees that although speed is desirable it is essential that we get the best and most authoritative advice on this problem

New Posts for Senior Registrars

Mr **KENNETH ROBINSON** asked the Minister of Health how *many specially designated senior registrar posts he intended* to approve, what guidance he was giving to regional hospital boards in this matter, and what would be the higher rate of pay attaching to these posts —Mr **DEREK WALKER-SMITH** replied The number of posts to be approved will be decided on merits after the boards' proposals have been received I am about to discuss with the Joint Committee the guidance to be sent to the boards Rates of pay will be a matter for negotiation

Miners' Boots

Mr **DERICK HEATHCOAT AMORY**, the Chancellor of the Exchequer, announced on April 29 that after considering the representations made to him he had decided to restore the exemption from purchase tax of miners' and quarrymen's protective boots and helmets

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Public Health

Vaccination against Poliomyelitis

A FIRST instalment of 2 million doses of Salk vaccine, tested and licensed for issue by the authorities in the U S A, is expected to reach this country next week This will be distributed at once Further batches of Salk vaccine both from new orders and from the pipeline under existing contracts will be arriving, and, according to the Ministry of Health, "there is every expectation that ample vaccine will be available to enable local health authorities and general practitioners to keep the vaccination programme going at full pressure"

Smallpox in Lincolnshire

ON May 4 a case of smallpox was confirmed at Scunthorpe in Lincolnshire The patient, a coloured man, working in a local steel works, was taken to Laceby Smallpox Hospital, near Grimsby

Infectious Diseases in England and Wales

Disease	Week ended April			
	5	12	19	26*
Diphtheria	2	4	1	3
Dysentery	1113	863	1010	927
Encephalitis				
Infective	6	3	5	3
Post infectious	2	4	1	3
Food poisoning	157	112	127	146
Measles, excluding rubella	4194	5066	5095	3916
Meningococcal infection	22	24	33	17
Ophthalmia neonatorum	35	23	23	26
Paratyphoid fever		2	4	3
Pneumonia, primary or influenzal	536	585	556	507
Poliomyelitis				
Paralytic	9	9	15	13
Non-paralytic		2	4	8
Puerperal pyrexia	162	244	173	211
Scarlet fever	857	738	600	628
Smallpox			1	2
Tuberculosis				
Respiratory	471	459	560	608
Meninges and C N S	3	9	6	12
Other	37	64	56	81
Typhoid fever	5	3	3	6
Whooping cough	515	495	539	655

* Not including late returns

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[1] See *Lancet*, May 3, 1958, p 971

Medicine and the Law

Without Prescription

A PATIENT was admitted to hospital on May 13, 1954, suffering from an attack of boils The house-surgeon in charge of her case ordered a course of streptomycin injections—thirty 0 5 g injections at intervals of eight hours The last injection should have been given at 10 P.M on May 23 In fact, the patient received four more injections than had been ordered, the final injection being given at 6 A M on May 25 On May 26 the patient experienced a sense of giddiness, and from that time she lost her sense of balance She brought an action claiming damages for negligence against the hospital management committee The committee denied negligence

Mr Justice STREATFEILD gave judgment for the patient and awarded her £3000 damages, having found that the ward sister had been negligent He said that it was impossible to approach the case without a feeling of deep sympathy for the patient, but the sole issue for him was whether negligence had been proved Though more was known about streptomycin today than in 1954, he had to judge the case through the spectacles of 1954 The matter for decision fell under three heads

First, had the house-surgeon been negligent in failing to observe the premonitory signs of streptomycin poisoning, or in failing to heed the patient's alleged complaints of giddiness? Secondly, had the nursing staff been guilty of negligence in the same respect? Thirdly, had the ward sister, or the two nurses, been negligent in allowing to be administered, or in administering, the four extra injections?

His Lordship acquitted the house-surgeon and nursing staff of any negligence under the first two heads Under the third, however, it was said that the ward sister and nurses were in breach of their duty not to administer streptomycin unless such administration was in accordance with the directions of a duly qualified medical practitioner The two nurses who had administered the four extra injections had done so without reason to suppose that the doses were other than those prescribed by a doctor Accordingly, they were not negligent.

It was apparent, however, that no precautions had been taken to ensure that the course of injections came to an end at the proper time. For this the ward sister must be held responsible she alone knew that the four extra injections exceeded the prescribed dose.

But did this amount to negligence in law? It would only be negligence if it could be shown that it was the four extra injections which had caused the damage and if the ward sister ought reasonably to have foreseen that damage might ensue On the evidence his Lordship was satisfied that it was the final injection that had caused the damage Accordingly she was guilty of negligence for which the committee could be made vicariously responsible Had a doctor in fact prescribed the additional injections which had in fact been administered, negligence might well not have been established, but the position differed where there had been no prescription To hold otherwise would be to deprive the patient of the protection of the trained mind of a doctor which the law sought to give, and possibly to enable a nurse to take it upon herself to administer streptomycin whenever she thought fit

SMITH v BRIGHTON AND LEWES HOSPITAL MANAGEMENT COMMITTEE Streatfeild J May 1, 1958 John Harrington Q.C., and Hugh Galpin (Bischoff & Co for Burnand & Burnand, Hove) Stanley Rees, Q.C. and J R. Cumming Bruce (Hempsons)

DAVID CALCUTT
Barrister-at-law

Diary of the Week

MAY 11 TO 17

Monday, 12th

Postgraduate Medical School of London, Ducane Road, W 12
4 P.M *Dr Brian Ackner Depressive Illness II*

Wright-Fleming Institute of Microbiology, St Mary's Hospital Medical School, W 2.
5 P.M Prof J R Squire Hypogammaglobulinaemia—Clinical and Laboratory Studies on the Gamma Globulins

Institute of Laryngology and Otology, 330 Gray's Inn Road, W C 1
6 P M Dr Joel Pressman (Los Angeles) Clinical Anatomy of the Larynx in Relation to the Spread of Cancer

Tuesday, 13th

Royal College of Physicians of London, Pall Mall East, S W 1
5 P M Dr Paul Wood The Eisenmenger Syndrome, or Pulmonary Hypertension with Reversed Central Shunt. (First of two Croonian lectures.)

University of London
5 P.M (St Bartholomew's Hospital Medical College, E.C 1) Prof H Rocke Robertson (Vancouver) Venous Thrombosis

Royal Society of Medicine, 1, Wimpole Street, W 1
5 45 P M *Experimental Medicine & Therapeutics Neurology* Prof G Payling Wright, Dr D R Laurence, Prof. E B Adams, Dr A Crampton Smith Tetanus
8 P M *Psychiatry* Dr Anna Freud Clinical Studies in Psychoanalysis

Guy's Hospital Medical School, London Bridge, S.E.1
5 P.M Prof A G Brom Recent Developments in Cardiac Surgery (Carbutt lecture)

Institute of Obstetrics and Gynæcology, Hammersmith Hospital, Ducane Road, W 12
2 P M Prof W C W Nixon An Integrated Obstetric Service.

Institute of Dermatology, Lisle Street, W C.2
5 30 P M Dr R G Cochrane Leprosy

University of Birmingham
4 P.M (Medical School) Prof J S Mitchell Studies in Radiotherapeutics (First of three William Withering lectures)

Wednesday, 14th

Royal Society of Medicine
2.30 P.M *Proctology* Dr Ronald Jarman, Dr Frankis Evans, Mr Gordon Ramsay, Mr J M Davis, Mr Innes Williams, Mr C I Cooling Complications of Excision of the Rectum

Postgraduate Medical School
4 P.M Prof Jan Waldenstrom Carcinoidosis and Some Allied Conditions

Institute of Diseases of the Chest, Brompton, S W 3
5 P M Dr. Lynne Reid Mucus Secretion in Normal and Morbid Lung

Institute of Laryngology and Otology
5.30 P M Mr I R H Kramer Giant Cell Diseases of the Oral Cavity

Institute of Dermatology
5.30 P.M Dr Cochrane Leprosy

University of Birmingham
4 P M Professor Mitchell Studies in Radiotherapeutics (Second William Withering lecture)

Thursday, 15th

Royal College of Physicians
5 P M Dr Wood The Eisenmenger Syndrome, or Pulmonary Hypertension with Reversed Central Shunt. (Second of two Croonian lectures)

Postgraduate Medical School
4 P.M Prof G M Wilson Simple and Malignant Goitre

British Institute of Radiology 32, Welbeck Street W 1
8 P M Prof F S Dainton Radiation Chemistry in Retrospect and in Prospect (Silvanus Thompson lecture)

Royal Society of Tropical Medicine and Hygiene, 26, Portland Place, W 1
7.30 P.M. Dr J R. Audy The Localisation of Disease, with special reference to the Zoonoses

Hypnotherapy Group
8 P M. (1, Wimpole Street, W 1) Dr David Stafford Clark, Dr T A Kemp Dr William Moodie Anxiety

Nuffield Orthopædic Centre (Wingfield-Morris Orthopædic Hospital), Oxford
8 30 P M Mr I S Smillie Loose Bodies in Joints

University of Birmingham
4 P.M. Professor Mitchell Studies in Radiotherapeutics (Last William Withering lecture)

Friday, 16th

University of London
5 30 P.M (London School of Hygiene and Tropical Medicine, Keppel Street, W C.1) Dr Ludwik Gross (New York) Viral Aetiology of Mouse Leukæmia—Its Possible Implications for the Problem of Cancer

Royal Society of Medicine
5 P M *Epidemiology & Preventive Medicine with the Fever Group of Society of Medical Officers of Health* Dr A M-M Payne (Geneva), Dr J C McDonald The Asian Influenza Epidemic, 1957

Postgraduate Medical School
10 A.M Mr I S R Sinclair Surgical Aspects of Pancreatic Disease

St Mary's Hospital Medical School, Paddington W 2
5 P M Dr R R. Willcox Gonorrhœa in Gynæcological Practice

Faculty of Radiologists
4 45 P.M (Royal College of Surgeons, Lincoln's Inn Fields W C 2) Prof D W Smithers Tumours of the Thyroid in Relation to Some General Concepts of Neoplasia (Knox lecture.)

Institute of Obstetrics and Gynæcology, Chelsea Hospital for Women Dovehouse Street S W.3
4.30 P.M Mrs D M Shotton Pelvic Tuberculosis

Notes and News

EMPIRE RHEUMATISM COUNCIL

Last year the Council appealed for £250,000 to finance a ten-year programme of intensified research This year at the annual general meeting, held in London, Dr W S C Copeman the chairman, reported that, though £175,000 was still urgently needed, with the funds that had been received the Council's activities had been extended, and the Council had endowed for ten years a new chair of rheumatology in the University of London at the Postgraduate Medical School[1] The Council has already endowed a chair at the University of Manchester

Two research fellows have this year completed their work for the Council Dr J K Norymberski, whose biochemical studies of the steroids are already being put to practical use in measuring chemically the effect of hormone remedies, and Miss I H Muir, who isolated chondroitin sulphate, which is present in connective tissue and joints The Council's trials of drugs continue Nine centres took part in a three-year trial comparing the long-term effect of cortisone and aspirin in the treatment of rheumatoid arthritis,[2] and a trial of gold therapy for arthritis is at present being carried out at 27 centres The Council's mobile field unit, which is the only one of its kind in the world, has had an active year, and Dr J S Lawrence, the director, reports the start of two genetic surveys The first has already produced interesting and unexpected results suggesting that there may be two forms of rheumatoid arthritis, one with and one without hereditary characteristics Random sample studies show that, contrary to general belief, rheumatoid disease may be present as a disorder of the cervical spine The second genetic survey, on the relatives of patients with multiple osteoarthritis, is still in its early stages, but preliminary results show a definite familial trend At the West London Hospital, under Dr J D Robertson, a biochemical test has been adapted to control the use of adrenocortical hormones As a result it has been found that only initial doses need be high, and that patients may continue their treatment at home under out-patient supervision

NEUTRALITY OF MEDICINE IN WAR

In Paris from June 5 to 7, with the President of the Republic as patron, will be held the Congres International de la Neutralité de la Médicine en Temps de Guerre

Outlining the policy of the committee, founded in 1952, which has taken the initiative in France, Prof Charles Richet, its president, says that the first duty of doctors, in war as in peace, is to save life In the second world war there were some 30 million deaths in Europe, and half of these were "useless" they could have been avoided without affecting the course of events The measures most important for reducing the brutality of war are those laid down by the International Committee of the Red Cross enemy prisoners and wounded must be treated as human beings, with humanity, and civilians in occupied regions have the same right to protection as the prisoner-of-war The Geneva conventions must in future be made more widely known so that they can be less easily violated In each country a group of doctors and of jurists who understand the conventions should be set up in time of peace, so that they can be sent immediately to places where fighting breaks out These groups should have a special international status, so that they will be accredited to all nations At present no country has at its disposal the body of doctors and lawyers whom it would need if it undertook the functions of a protecting Power—well-qualified volunteers who would be capable of taking over key administrative and medical posts in the country at war Perhaps most important in the long run, an intergovernmental organisation should at once be formed, able to draw on material and economic resources and a pool of medical personnel

"Take a possible case Two countries are at war After a fortnight there are, on each side, 500,000 casualties—wounded, shocked gassed, burned, infected How, with only their own doctors, can these countries cope with this situation? How, in a single country, can one find the 30–50 tons of human blood or plasma needed each day? The reserves of dressings and gas-gangrene serum and tetanus serum of one country may well be exhausted in a month To put it in another way, a country which is medically isolated could not give proper care, in war-time, to more than one casualty in three or four"

Medical aid from outside, given in the spirit of the International Red Cross, with the absolute impartiality which the Red Cross could assure, would relieve much suffering without affecting the outcome of the war and probably without prolonging it by a day Perhaps the seriously wounded and sick could be taken into hospital in neutral territories, and remain interned until hostilities cease If, as is possible, the war affected the whole world, the committees of doctors and jurists, with supranational status, would be morally neutral They would be in the best position to enable our shattered civilisation to survive

Particulars may be had from the Comité de la Neutralité de la Médicine en Temps de Guerre, 37, rue de Bellechasse, Paris VII

CANDIED SENIOR REGISTRARS

The difficulties of senior registrars are at the moment being discussed at the highest level A more unorthodox but no less discerning approach to their problems has been made by Edward Candy in his novel *The Graver Tribe*[1] He begins by describing the mixed feelings of disappointment and elation aroused by the appointment of the new surgeon at St Chad's hospital, and for good measure he includes the extramural problem of a marriage that has gone wrong and the ethical problem of whether it is right to operate on an unwilling patient even to save his life The reader may well have the uneasy feeling that the matron of St Chad's is Miss Compton Burnett in disguise, for both the staff and the patients speak with the stylised formality and devastating frankness of her characters But Mr (or is it Dr ?) Candy does not follow her practice of confining melodrama to the wings St Chad's is a lively hospital, and a young surgeon there thinks nothing of hurrying from the theatre where he has performed an emergency operation to the medical school where he wields a stomach pump on his alcoholic chief who has just attempted suicide

PREMATURE MARRIAGE

Delinquency and unhappiness are usually more dramatic, though less pleasant, than uneventful stable behaviour and happiness, and we are apt to forget that the bad publicity which young people too often receive today is earned by a small minority We are also apt to forget how often the unsatisfactory behaviour of even that small minority may be due to what Dr John Highet[2] lately described as a "barrage of potentially corrupting adult practices and influences" As examples of these he cited the emphasis on sex, glamour, sumptuousness, and luxury, on force, violence, deceit, and dishonesty, on the philosophy of "anything goes" and "nothing sacred" A recent survey[3] of 400 young people showed that nearly a quarter thought that there was nothing wrong in an engaged couple having sexual intercourse Again in recent years official reports show that 2 out of every 3 first babies born to brides aged sixteen to nineteen were conceived out of wedlock These extramarital conceptions are one reason for the present trend toward earlier marriage In Scotland 1 bride in 7 is under twenty and 1 in 4 is under twenty-one, while the proportions are even higher in England But many of these young people freely choose to marry young, perhaps understandably in view of the emphasis which is laid on sex in the world in which they live Another factor in Dr Highet's view is what he terms the "irresponsible" recommendation of early marriage by some doctors This recommendation, he suggests, is based solely on the ground that it is best for a young woman to start her

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[1] 21st annual report of the Empire Rheumatism Council Faraday House, *8 Charing Cross Road London W C 2*

[2] See *Lancet*, 1957, ii, 1327

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[1] London Gollancz 1958 Pp 204 12s 6*d*

[2] In an address to the Scottish branch of the Red Cross Society on March 29 Dr Highet is lecturer in sociology in the University of Glasgow

[3] Church of Scotland Youth Committee Youth at Leisure Edinburgh 1956

family as early as possible. But there is another side to the picture, and he believes that it would be a real service to point out to young people that it has been estimated [4] that, if recent trends continue, then on the average 1 in 4 of the girls now marrying between sixteen and eighteen years of age will have been divorced by the twentieth anniversary of their marriage, compared with 1 in 10 marrying between nineteen and twenty-two and 1 in 16 marrying between twenty-three and twenty-seven.

MARGARET DE SOUSA DEIRO FUND

The scope of this fund, which was set up to help indigent gentlewomen with early pulmonary tuberculosis, has lately been widened by an order of the Charity Commissioners, and the trustees may now apply any income not needed for the original purpose to the care, reablement, and aftercare of indigent women with pulmonary tuberculosis or any other disease of the chest

The fund can make grants to cover the cost of treatment, when this cannot be carried out in suitable conditions under the National Health Service, and grants towards convalescent holidays after institutional treatment. In approved cases the trustees can also give financial help for reablement and convalescence. By its constitution the fund is unable to help patients with chronic illness who have no prospect of returning to employment. Further particulars and application forms can be had from the trustees, 1, New Court, Carey Street, Lincoln's Inn, London, W C.2.

MEDICAL FILMS

A NEW film, *The Treatment of Sports Injuries* (16 mm, sound, colour, 22 minutes, Great Britain, 1957), is of special interest to school doctors and those associated with sports clubs

The film opens with the statement that most sports injuries, given adequate first-aid, treatment, and rehabilitation, recover rapidly The causes of injuries are direct and indirect trauma, strong muscular contraction, and postural strain, and their treatment consists primarily in the control of bleeding and support of the injured part. Recovery depends as much on the effort of the patient as on the treatment by the doctor The management of a sprained ankle is shown in detail The second half is devoted to specific lesions, including knee injuries sustained in cricket, ski-ing, and football, tennis-elbow, and a tear of the hamstring muscles of athletes The film ends with a summary and a call for closer cooperation between the doctor, the hospital, and the trainer of sportsmen, not only in the treatment, but also in the prevention of injuries

Although some may disagree with certain details of treatment, the principles are sound and the emphasis on home exercises and on the value of supervising correct posture during training is noteworthy

Copies of the film are available, free of charge, from T J Smith & Nephew, Ltd, Medical Department, Neptune Street, Hull

The Grand Rounds—1 Acute Abdominal Problems (16 mm, sound, black and white. 57 minutes, U S.A, 1956) is one of two film records of American television discussions now available in this country Three abdominal surgical problems are considered

The first case was of a man with a long history of asthma and bronchitis, severe scoliosis, and upper abdominal pain of recent onset Film taken when he was admitted to hospital was shown and radiographs and laboratory findings were presented After discussion by the panel of various diagnoses, film taken at operation was shown, and the results and postoperative course were debated The second case was a man who had been admitted with an inflammatory condition of his face and an upper respiratory infection He had subsequently collapsed and a mass was detected in the left upper quadrant of his abdomen The diagnosis was discussed and the results of laparotomy are revealed The third case was of a man, aged 71, with a long history of peptic ulcer and increasing pyloric obstruction who had been admitted to hospital two weeks previously with a perforation of his ulcer This had been treated conservatively with success until that morning when the patient had had a severe hæmatemesis The ensuing discussion dealt with the conservative treatment of perforations—described as 'widely practised in England'—the effect of long-continued gastric intubation, the incidence of hæmorrhage as a complication of perforations in the elderly, and the course to be followed in this case.

This is an interesting record from which some valuable diagnostic points may be gleaned The discussion by the experts is lively and stimulating, and Dr Leo G Rigler's analyses of the X rays are informative

In the second film, *The Grand Rounds—2 The Cardiac Patient in Stress, Work, Surgery Pregnancy* (16 mm, sound, black and white, 90 minutes, U S A., 1956), a further three cases are discussed.

The first case was of a man who four and a half years earlier had been admitted with upper abdominal distress for cholecystectomy, but had had a cardiac infarction before the operation After the panel had discussed the argument for elective cholecystectomy, the patient was taken to the operating-theatre, where the anæsthetist discussed the anæsthesia for such a case A debate on postoperative management followed The second case was of a woman, aged 35, in the fourth month of her seventh pregnancy with signs of mitral and aortic stenosis Her heart sounds were demonstrated with an amplifying stethoscope and her radiographs were shown The panel discussed various aspects of cardiac disease in pregnancy and labour The third case, of a man with a cardiac infarction, stirred up a provocative discussion on management of cases in which opposing views were expressed by Dr Sam Levine and Dr Paul Dudley White

These films are well worth showing to any group of physicians and surgeons, and medical students may find the diagnostic problems useful

They may be borrowed, free of charge, from Upjohn of England, Ltd, 4, Alford Street, London, W 1

University of Cambridge

On April 26 the following degrees were conferred

M Chir —I W Broomhead *W K. Douglas.
M.B, B Chir —*A. D H. Pooler
M.B —J N Stenhouse

* By proxy

Guy's Hospital Medical School

Prof A. G Brom will deliver the Carbutt lecture on Tuesday, May 13 He is to speak on recent developments in cardiac surgery Dr Hugh B Cott will give the Fison lecture on Friday, May 30 His subject will be protective coloration in animals Both lectures will be held at 5 P.M at the school, London Bridge, S E 1, and tickets may be had from the dean.

Charing Cross Hospital Medical School

Sir Howard Florey will deliver the Huxley lecture at the school, Chandos Place, London, W C 2, at 5.30 P.M, on Thursday, May 22 He will speak on the changing emphasis in medical research

Institute of Cardiology, London

Dr Howard Burchell of the Mayo Clinic, Rochester, Minnesota, will give the St. Cyres lecture for 1958 at 1, Wimpole Street, W 1, on Wednesday, June 4, at 5 P M. He is to speak on pulmonary hypertension in congenital heart-disease

Ciba Foundation

The trustees of the Ciba Foundation are offering in 1959 not less than five awards (£300 each) for investigations into the basic problems of ageing Entries must reach Dr G E. W Wolstenholme, director of the foundation, 41, Portland Place, London, W 1, not later than Jan 1, 1959

The Foundation's lecture on research on ageing will be given this year by Prof F Bourliere of the Laboratoire de Physiologie Faculte de Medecine de Paris, on Thursday June 19, at 5 P.M., at the Royal Institution, 21, Albemarle Street, London, W 1 He is to speak on the comparative study of age changes

Simpson-Smith Prize

As the subject for this prize for 1959 the Institute of Child Health has chosen Spina Bifida.

The prize (100 guineas) is open to men and women from the British Commonwealth or the Republic of Ireland who are engaged in the practice of surgery A copy of the rules can be had from the secretary of the Institute, The Hospital for Sick Children, Great Ormond Street, London, W C 1 Essays must be submitted not later than Dec. 31, 1959

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[4] Registrar-General's Statistical Review of England & Wales, 1946-50 Text Civil, p 66

International Congress of Clinical Pathology

This congress will be held in Madrid from June 13 to 17, *1960* Further particulars may be had from *Dr José Aparicio Garrido, Facultad de Medicina, Pabellón Nr 2, Ciudad Universitaria, Madrid*

Marlborough Day Hospital

On Monday, May 19, at 8 15 P M at the hospital, 38, Marlborough Place, London, N W 8, Dr E M Bluestone, formerly director of Montefiore Hospital, New York, will speak on social psychiatry

Work Study in the Hospital Service

The Chartered Society of Physiotherapy is arranging a conference on this subject, to be held on Oct 17 and 18 at the Westminster Medical School, S W 1 Further particulars may be had from the secretary of the society, Tavistock House (South), Tavistock Square, W C 1

Royal Institute of Public Health and Hygiene

Dr B G B Lucas will give the Bengué lecture for 1958 on Oct 20, at 5 P M His subject will be artificial aids in the control of the circulation Brigadier J S K Boyd will give the Blackham lecture for 1958 on Tuesday, Nov 11, at 4 P M on yellow fever and its prevention Both lectures will be given at the institute, 28, Portland Place, London, W 1

Centenary of Babinski

The Société Française de Neurologie, at its Réunion Neurologique Internationale in Paris on June 2, is celebrating the centenary of the birth of J Babinski

The president, Prof Raymond Garçin, will speak on Babinski's work, *Sir Francis Walshe on his place in modern neurology,* and A Tournay on Babinski the man The two ensuing days will be devoted to a symposium on the cerebellum

Legislation on Mental Health

Opening the annual conference of the Institute of Hospital Administrators in London on May 4 (*The Times*, May 5), Mr Derek Walker-Smith, the Minister of Health, reaffirmed the Government's acceptance of the need to revise the law relating to mental health They intended, he said, to promote legislation as soon as possible, though not in the current session of Parliament He hoped that from the discussions on the Royal Commission's recommendations there would emerge a new and improved pattern of hospital administration

College of General Practitioners

Applications are invited, before Sept 1, from members of the college for not less than fifteen Upjohn travelling fellowships of up to £200 each in value

The object of these fellowships is to enable general practitioners to undertake postgraduate study (for at least two weeks) at their old teaching hospitals or at any other hospitals, clinics, health centres, or general practices of their choice They are to be presented annually, by Messrs Upjohn of England Ltd, to members of the college who are in active general practice in the United Kingdom or Eire Further particulars may be had from the secretary of the college, 41, Cadogan Gardens, London, S W 3

Royal Commission on Remuneration

The Royal Commission on Doctors' and Dentists' Remuneration were taking evidence last Thursday, May 8, from representatives of the Society of Medical Officers of Health and the Association of County Medical Officers of Health of England and Wales

On May 15, representatives of the Medical Research Council, and the Committee of Vice-Chancellors and Principals of the Universities of the United Kingdom have been invited to attend

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A 16 mm film, entitled *The Hypnotic Treatment of Psychogenic Illness*, has been made at Belmont Hospital, Sutton, Surrey It may be borrowed free of charge by hospitals and medical societies on application to the group secretary at the hospital

Dr H Seaward *Morley* has been appointed a member of the council of the Board of Registration of Medical Auxiliaries

The flag day for the National Association for *Mental* Health and the *Mental* Health Research Fund joint appeal will be held this year on Tuesday, July 8, in the *Metropolitan* boroughs

A symposium on carcinoma of the lung was held by N A P T in London last November, the proceedings have been published as a booklet (pp 48, 6*s*) obtainable from N A P T, Tavistock Hous North, Tavistock Square, London, W C 1

The *Bishop of St* Edmundsbury and Ipswich will dedicate a memorial garden at Golders Green Crematorium to the memory of the late Lord Horder on May 30, at 3 P M Invitations may be had from the secretary, The London Cremation Company Ltd, 45, Nottingham Place, London, W 1

The United Hospitals' Choir, which rehearses on Thursday evenings at St James's and St Peter's School, Great Windmill Street, London, W 1, invites new members to join Further details may be had from the secretary, Miss J Magrath, 18, West Side, Clapham Common, London, S W 4

The annual dinner of the Indian Medical Service Dinner Club will be held at the East India and Sports Club Limited, St James's Square, London, S W 1, on Friday, June 13, at 7 30 P M Tickets may be had from the secretary of the club, Medical Board Room, Commonwealth Relations Office, Matthew Parker Street, S W 1

St John's Wood Church, London, N W 8, has chosen this year as the theme of its World Church weekend, on May 10 and 11, the Church and Disease The speakers will include Dr Desmond O'Neill, and the programme ends with a discussion on "What's it got to do with me?" in which a surgeon, a general practitioner, *a children's officer, and a committee member of the St Marylebone* Almshouses and Housing Associations will take part

The first issue of *District Nursing*, the official journal of the Queen's Institute of District Nursing, has appeared The new publication, which has taken over the old *Queen's Nurses' Magazine* with a view to developing its scope, intends, in its own words, "to meet the needs of the technical and administrative worker in the domiciliary health field" It is to be published monthly and costs 1*s* The editorial offices are at 57, Lower Belgrave Street, London, S W 1

CORRIGENDA *Slough Industrial Health Service*—In a note on April 26 (p 917) we stated that the occupational hygiene service was controlled jointly with the London School of Hygiene and Tropical Medicine We are informed that control now rests wholly with the Slough Industrial Health Service

Fat-mobilising Activity of Human Urine—In fig 3 of the article by Dr T M Chalmers and his colleagues (April 26, p 866) the specific activity as percentage of control was mean ±2 S E M and *not* mean ± S E M

Appointments

BARTLET, J E A, M D Aberd, M R C P, D P M consultant psychiatrist and medical superintendent, Exminster Hospital, near Exeter

DAVIDSON, A L M, M B St And senior casualty officer, County Hospital, Lincoln

FOSTER, J C, M B Edin, F R C S E orthopædic surgeon (S H M O), East Cumberland group of hospitals

LEONARD, T F, M B N U I, D P H assistant M O and school M O, Warrington

PAGAN, R T, M B Lond assistant M O H and school M O, Smethwick

SCHOFIELD, C B S, M D Durh assistant venereologist (S H M O), Newcastle upon Tyne group of hospitals

SHARP, C J, M B Leeds, D O assistant ophthalmologist (S H M O), Sunderland and Hartlepools group of hospitals

Manchester Regional Hospital Board

GORDON, N S, M D Edin, M R C P consultant neurologist, Booth Hall Hospital, Manchester, and Royal Children's Hospital with additional duties at *David Lewis Epileptic Colony* Cheshire, and Preston Hospital Centre

HALNAN, K W, M D Cantab F F R D M R T assistant radiotherapist (S H M O), Christie Hospital and Holt Radium Institute

SHERRAH-DAVIES EVAN M B Cantab, F R C S, D M R T consultant radiotherapist, Christie Hospital and Holt Radium Institute

Welsh Regional Hospital Board

ANSARI, A H, M A Cantab, M R C S, D M R D consultant radiologist based at Royal Gwent Hospital Newport

BIHARI JULIAN, M B *Lond*, F R C S D L O consultant E N T surgeon, Mid-Glamorgan H M C area

HOWELL, R G, M B Oxon M R C P consultant dermatologist based at Neath General Hospital Glamorgan

PILLAI, SUNDRAM M B Rangoon F R C S D O M S, D L O consultant ophthalmologist, West Wales H M C area

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SOME PATHOLOGICAL ADAPTATIONS IN THE PERIPHERAL CIRCULATION*

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ADAPTABILITY, in living organisms, is a prerequisite of survival It is fundamental to the doctrine of natural selection, and on the smaller stage of the human species it is a daily experience Within the yet narrower compass of the bodily economy the same truth holds and persists, though in less obvious fashion, down to the ultimate constituents of the body—the cells

The cell is in many cases more adaptable than the organ of which it is a part, and the organ than the body as a whole The survival and execution of the functions of cells depend upon the circulation The circulation has three main parts the cardiac pump, the conduit tubes, arteries and veins, and the metabolic area, the capillaries A great deal has been discovered about the adaptability of the heart, but rather less about that of the conduit system, whilst the changes in the capillary area—in a sense the latest comer in the field of physiological research —are still less completely known

When we pass across the grey band which divides what is physiological from what is pathological, and enter the dark area which is the true domain of pathology, we are in a territory full of pitfalls and quagmires The investigator faces the double difficulty that he has both to try to find out the anatomical changes in an organ—changes which essentially are not static but increase with disease and decline with recovery or become adapted to a permanently abnormal state of affairs—and to interpret these as effects in the organ and the body In pathological investigation, as is logical, anatomy has generally led physiology, and in what I have to say I shall be concerned chiefly with anatomical changes

I am very conscious that my discourse may contain more of speculation than Matthew Stewart would have approved by his own high standards, but it is my purpose to be suggestive rather than dogmatic and to deal with matters which cannot at the moment be regarded as settled

Hyperæmia and Ischæmia

The morbid changes in a system of conduits can result in a general way either in their widening or narrowing, and in a supply of either more or less blood Unfortunately for the investigator it is not as simple as this, since "blood" is not a substance of constant composition, nor are the tubes through which it flows of fixed size, structure, or function The blood is varying all the time it is making the circulatory circuit, and (what is more) *it is varying at* different and inconstant rates and travelling at different and variable speeds

In an attempt to simplify the matter—for it is the aim of the scientist to reach general principles—we ignore much of this and roughly divide the conditions we encounter into *hyperæmia* and *ischæmia* The former we subdivide into *active* and *passive*, and the latter into *acute* and *chronic* In this lecture I am concerned essentially with the arterial side of the system, so we need consider only active hyperæmia and ischæmia Active hyperæmia is due to relaxation (local or general) of the arterioles, ischæmia to functional constriction or anatomical occlusion

Active Hyperæmia

Hyperæmia is an important part of the inflammatory reaction, but with this aspect of it I do not intend to deal The condition of chronic active hyperæmia, meaning an excessive supply of fully oxygenated blood to tissues having normal requirements, is a rarity and intrigued the great John Hunter as a possible cause of hypertrophy It certainly occurs with increased demand in hypertrophy, but it seems to be secondary, or at most coincidental It is sometimes seen in malignant growths, as for example in certain acute carcinomata of the breast and in some sarcomata which have many of the features of acute inflammation and are characterised by very rapid growth An obvious case of such a condition, occurring without abnormal tissue demands, would seem to be arteriovenous fistula, but this is not really admissible, since it involves complicated changes on the venous side producing abnormal pressure in the venous system and symptoms of chronic venous congestion Nevertheless the skin temperature is raised in the chronic phase, there is an increase in the size of the limb, and, if the fistula is present before the epiphyses have united, the length of the bones is increased

It might be thought that the effects of chronic active hyperæmia could be produced by keeping animals in an atmosphere of increased oxygen tension for long periods, but this gives no answer, because damage to the lungs results and causes death with pneumonic changes which produce anoxia Similarly, in local venous obstruction, such as may result from destruction of the venous valves, the picture is complicated by stasis, and here too we cannot disentangle the effects of anoxia

I would, however, like to quote a rather remarkable case I saw recently

A man of about 50 had his left leg flexed and useless for many years from some chronic local venous disease, which for the past three years had been complicated by ulceration The venous valves were destroyed by old thrombophlebitis There was chronic osteomyelitis of the lower ends of the tibia and the fibula with much formation of new bone The skin over his leg was ichthyotic In spite of prolonged disuse this leg was larger than its fellow, which appeared quite healthy and on which the patient walked, and arteriography showed all the arteries in the diseased limb to be unusually dilated The increase in size of the disused calf-muscles was not due to muscular hypertrophy but to a great infiltration with fat between atrophied muscle-bundles—so much so that a transverse slice of the leg, including the bones, floated

This recalls the appearance of the leg muscles in pseudohypertrophic myopathy in children The factors which lead to the latter disease are unknown, but the present case may provide a pointer, in that we had a combination of disuse plus chronic active congestion in the arterial circulation, the latter presumably due to the chronic inflammation in the bones, together with venous stasis

Ischæmia

When we come to consider ischæmia, the problem is more manageable, since from its nature it is so often associated with arterial disease It is essentially a process which manifests itself at the periphery of the arteriolar/

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* Matthew Stewart memorial lecture given in Leeds on Nov 28, 1957

capillary system This, I should point out, is not synonymous with the extremities or with the body's surface The peripheral part of the liver's circulation, for example, is at the centres of the lobules, and of the kidney at the glomerular tuft and just beyond The extremities and the skin, however, attract our special attention because the main effects of ischæmia—colour changes, pain, œdema, hæmorrhage, and eventually necrosis—are most readily seen and experienced there

Acute peripheral ischæmia—Grave ischæmia may occur without anatomical arterial disease, as a result of peripheral spasm We are all acquainted with physiological degrees of this in cold fingers and toes, and with more severe grades in chilblains and frostbite A special case is the Raynaud phenomenon, where it is suggested that there is some unexplained oversensitivity to cold in the digital arteries Acute peripheral ischæmia resulting from central circulatory deficiency, severe enough to produce gangrene, is sometimes seen and was mentioned by Paget in 1853, when he wrote of a man who cut his throat and lost so much blood that "the nutrition became impossible in one of those parts to which blood is more difficultly sent, and before he died his nose sloughed" Brodie speaks of a drunken man who "being bled to an inordinate extent was seized with gangrene of both feet" Such an acute condition was recently encountered in the case of a man of 62, suffering from left ventricular failure and coronary disease, who developed gangrene of the nose and the left ring-finger, with early gangrene of other fingers Here we had some information about the deep peripheral circulation, since the effective renal blood-flow was measured at the time and found to be only 34 ml per min (normal 700 ml per min) At postmortem examination advanced stasis was found in the glomerular capillaries, similar to that which precedes symmetrical renal cortical necrosis In another case, in a young woman, this renal condition was fully developed, along with gangrene of the nose, cheeks, and fingers These are special examples of acute peripheral ischæmia severe enough to cause necrosis but not due to any organic primary peripheral vascular disease

Chronic peripheral ischæmia—The basis of chronic ischæmia is in the arterial system, and the most common cause is narrowing of the arteries due to atherosclerosis and its effects

Degeneration or Incrustation?

For almost a hundred years the teaching of Virchow dominated our ideas on the genesis of atheroma, but recently the whole of this has been called in question by Duguid, who has revived and re-presented in modern form the earlier view of Rokitansky—that the atheromatous plaque (the hallmark of the disease) is an "incrustation" on the inside of the artery Virchow held that it was a degeneration in the intima with lipoid deposition and that the other changes were secondary to this Duguid regards a thrombus as the starting-point and illustrates its development in the way shown in his papers (1949 et seq) These views have aroused great interest, and I should like to consider them briefly, and especially the objections that have been raised against this simple explanation

(1) It has been asked why, if a thrombus becomes an atheromatous plaque, do we so commonly see quite a different condition developing from a thrombus—often alongside an atheromatous plaque (fig 1), an appearance well known to pathologists? I shall leave this point for the moment and come back to it later, for it is fundamental to much of what I have to say on this matter

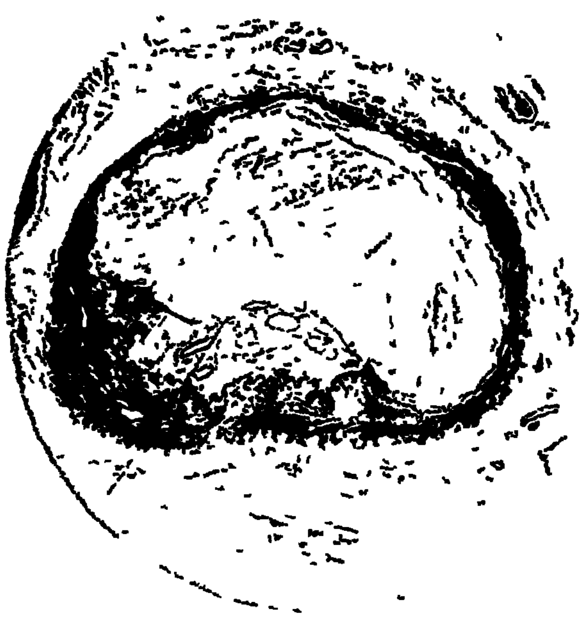

Fig 1—Atherosclerosis, followed by thrombosis and canalisation in anterior tibial artery Note internal elastic lamina opposite recently canalised area and its absence opposite older atheromatous lesion (×15)

(2) How are we to explain the great accumulation of lipoid substances in the plaque—a quantity which is often far greater than can be formed by the breakdown of a local thrombus? This difficulty is common to either theory The lipoid has to come from outside, and the mechanism may be the same in either case The point gives us no assistance But I think it is associated with one or more red herrings—if I may introduce such a metaphor—which have helped to maintain Virchow's view

(1) There is the association between atheroma and diabetes In the days before the discovery of insulin, diabetes was treated by a high-fat and high-protein diet and carbohydrate starvation Under such a regime heavy lipæmia was a common result, and diabetics showed extensive atheromatous lesions with heavy accumulation of lipoids I believe the explanation to be not that the atheroma was caused by the lipæmia but that —diabetes being a disease in which lipoids tend to accumulate —this feature was favoured and exaggerated by the abnormal quantities of lipoid in the blood and tissue fluids

(b) The second red herring was the discovery that by feeding rabbits on large amounts of cholesterol, lesions resembling atheroma could be induced in the aorta More critical analysis has shown that the analogy is not really very close, and these investigations have contributed little if anything to the solution of the problem Under modern treatment of diabetes I think we must review the association between the diseases My own experience, over the past twenty years, has been that diabetics do not come to operation for ischæmia due to atheroma any earlier than non-diabetics (71 5 and 71 years respectively), and on such a basis there are no grounds for believing that peripheral vascular disease is influenced by diabetes

(3) Why are there no iron salts in a formation claimed to have developed from a thrombus?

(4) The fate of arterial thrombi in a disease in which they are a main feature—Buerger's disease—is very different

(5) Thrombi in veins only rarely develop into atheromatous plaques But veins have quite a different anatomical structure and lack the features which, I suggest, play a part in the formation of the plaque

The Thrombus and the Reaction

I believe that the truth of the matter lies with Duguid, and that the difficulties I have mentioned are answerable and are related to the nature and composition of the "thrombus", and to the vascular reaction In fact, if we meet the first of these objections we have the answer to most of the others

There is no doubt that we can find abundant evidence that certain thrombotic masses can be incorporated in the vessel wall and give rise to lesions indistinguishable from atheromatous plaques

Figs 2 and 3 show the popliteal artery of a man of 42 with Buerger's disease, with a thrombus extending down as far as the anterior tibial artery The thrombus which only partially occludes the vessel, has become covered with endothelium, and is in process of incorporation into the artery wall, being covered on its inner surface with a living cellular membrane formed in connection with the tunica intima Underneath there is a central formless mass corresponding to the necrotic centre of the atheromatous plaque, and we also see a "splitting" of the internal elastic lamina at the margin of the plaque, such as is so often figured in descriptions of atheroma. Beneath the thrombus the internal elastic lamina is still intact.

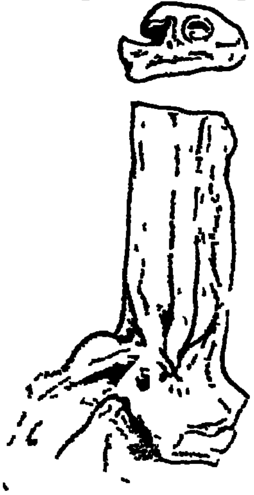

Fig 2—Thrombus, partially occluding tibiopopliteal trunk, becoming incorporated into lateral wall of artery in man aged 42, with Buerger's disease.

If we agree then that a thrombus can develop into a lesion having the histological characters of atheroma, we come back to the question Why do not all thrombi do so? The answer is the one I have already suggested—that this depends on the nature and completeness of the thrombus and the reaction of the arterial wall We are inclined to ignore the fact that "thrombi" vary greatly, from purely platelet thrombi to massive clots formed from whole blood and containing all its chemical and cellular constituents in approximately normal ratios I agree with Duguid, in his later papers, that it is not the gross thrombus, figured in his original paper, which ordinarily undergoes a metamorphosis into an atheromatous plaque the thrombus in which this change takes place is the one constituted mainly of fibrin and platelets, which is slowly deposited, is eccentrically placed, and may grow by slow accretion

We have learnt of late, to some extent since arterial grafts have come into use, the great growth activity of the endothelium which enables it to line a graft with great speed, and it is fair to assume an equal activity in the covering in of a mural thrombus I would modify Duguid's original diagram to one which takes rather more account of the activity of the endothelial tissue and of the vessel wall I think there is no doubt that the endothelium and cells associated with it can form reticulin and collagenous tissue

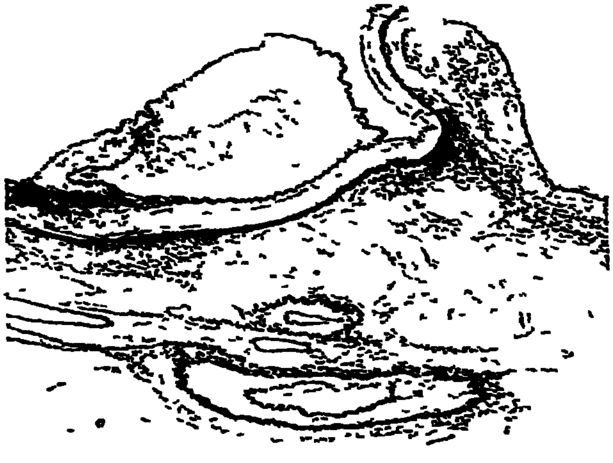

Fig 3—Section of same artery as in fig 2, showing incorporation of thrombus and formation of new elastic layers. (×6 5)

Organisation of Thrombus

Crawford and Levine (1952) have emphasised this, Geiringer (1951) has mentioned superficial giant capillaries proceeding for a short distance from the lumen, whilst Duguid (1949) speaks of the collagenous metamorphosis of the superficial layer of thrombus beneath the endothelium Under certain conditions this endothelial activity may be enormously extended and result in the canalisation of the thrombus (Dible 1958), but in the special type of mural thrombus leading to the formation of the atheromatous plaque the development ceases, unless further accretions form on the surface The atheromatous plaque, therefore, becomes as it were encapsulated and thrust aside from the lumen, and there is little or no persisting

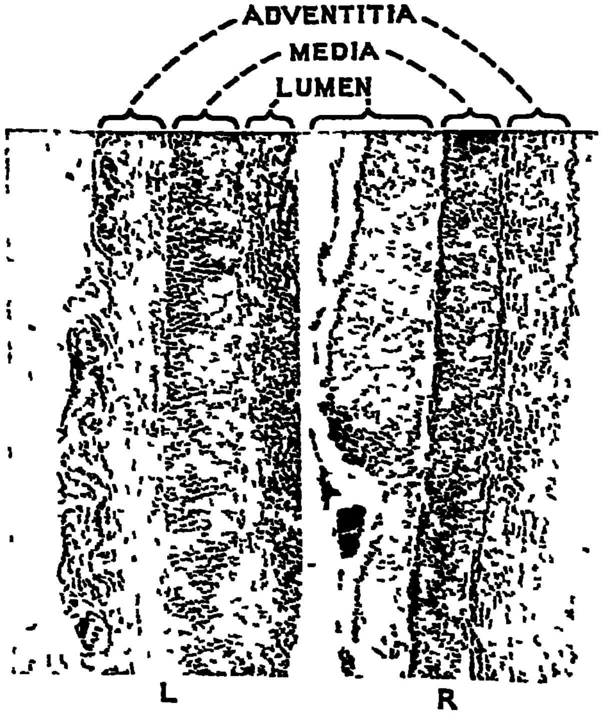

Fig 4—Two ulnar arteries from the same patient with (L) old canalising thrombus, and (R) very recent thrombus. Note increase in vasa vasorum of middle coat in left vessel and absence of such reaction in right. In spite of this vascular response vasa vasorum do not penetrate to thrombus (×36.)

stimulus to further change from the side of the lumen, but, if the area of narrowing is converted into a complete occlusion by the later formation of an acute thrombus, this will have a different fate Fig 1 shows the outcome of such a condition, but the second thrombus has undergone canalisation, which is quite another form of adaptation of the damaged circulation and a different pathological process, of which I shall speak in a moment

So far we have ignored the rest of the vessel wall The middle coat does not accept the presence of a thrombus passively but reacts, notably by an increased prominence of the vasa vasorum (fig 4), which in the case of atheroma show a limited tendency to vascularise the plaque But here there is an apparent barrier, and this, as I have suggested elsewhere (Dible 1958), seems to depend upon the presence of an intact internal elastic lamina I believe that, in a healthy vessel wall, this opposes an impassable bar to the ingrowth of vessels from the media, but in the depths of the atheromatous patch the lamina commonly breaks up or disappears as the patch grows older, with the result that the barrier is removed and some vascularisation of the patch may be seen on its deep side

A good deal of attention has been paid, notably by Winternitz et al (1938), to hæmorrhages into the depths of atheromatous plaques in the coronary arteries The more advanced of these invading vessels have a capillary structure and may be the source of hæmorrhage, which seems particularly liable to occur in a pulsating vessel containing rigid and sometimes calcified plaques, in which sheering strains would tend to develop

Canalisation of Thrombus

In dealing with the possible and limited vascularisation of the atheromatous plaque I have been leading up to the quite different fate which an intra-arterial thrombus may undergo—a thrombus such as I have visualised as finally occluding our narrowed atheromatous vessel (fig 1), or produced in the healthy artery of a young person, or as develops in Raynaud's disease

The expression "organisation" is often used in connection with the changes in an occluding thrombus—I think not wholly accurately, for the process is not exactly comparable to the conversion of a fibrinous exudate, or a mass of effused blood, into living fibrous tissue, such as is seen in the organisation of a fibrinous pericardial exudate The result of organisation is a scar it is a form of healing in which a minimum of new fibrous tissue is formed, with the requisite minimum of vessels to nourish it derived from the existing blood-vessels of the part In such a process in an artery the thrombus would be converted into a plug of fibrous tissue, with its own little circulation supplied by the arteries of the vessel wall and returning its blood to the veins of the vasa vasorum But is this what happens? No, we find a development of new blood passages and vessels within the thrombus, quite independent of the vasa vasorum And why is this? We have to remember that an artery has two sources of blood-supply, and that these are functionally independent The one is from the contained blood, and the other, to the major part of the wall, comes from adjacent small arteries but not directly from the main vessel The fact that these vasa vasorum come from smaller adjacent arteries means that the blood is supplied at a suitably reduced pressure It seems to me that these two divisions are functionally and anatomically independent, and that their territorial demarcation in medium muscular arteries corresponds to the internal elastic lamina I am not prepared to say whether this is an actual anatomical barrier or whether it merely corresponds to a physiological demarcation all I know is that it appears to exist

We know that intravascular occluding thrombi undergo this canalisation, and the evidence of histology is that these are through vessels which do not communicate with the vasa vasorum In fact if they did, and blood at high pressure from the lumen of a large artery were to pass directly into the small vessels in an organised thrombus, very abnormal hæmodynamic conditions would probably arise, and possibly the flow in the arteries of the vasa vasorum concerned might be reversed, and a direct arteriovenous communication develop with the veins of the arterial wall On the other hand, the exposure of these through channels to the full pressure of the blood in the occluded artery has the beneficial effect of distending them

I therefore conclude that the canalisation of a thrombus is a wholly different process from its organisation—different in its mode of development, the vessels involved, *and its purpose and effect* *The purpose of canalisation* is to restore as far as possible a through circulation, and this may be accomplished to various degrees Elsewhere I have illustrated the condition in canalised arteries and have described the stages of its development (Dible 1958)

The development of this new system of vessels within the boundary of the internal elastic lamina may take place from mesenchymal lining cells of the tunica intima but may also be contributed to by cells present in the circulating blood Such vessels are independent of the intrinsic circulation in the middle coat, and an important point in support of this argument is that the newly formed canalising vessels not only lie inside the internal elastic lamina but also are oriented in the direction of the artery's lumen, whereas the vessels in the middle coat of the artery's wall are oriented at right angles to these, and the two circulations do not communicate

But do the vasa vasorum play no part? I said earlier that they react to the presence of a thrombus, and this is so Their increased development, which is so obvious in fig 4, may well be due in part to the effect of the thrombus in cutting off the nutrition of the parts of the arterial wall nearest to the lumen, which are normally nourished by imbibition And I believe that their function is limited to this, at any rate in the beginning I do not deny that they may eventually penetrate the thrombus, but this appears to be a late change, associated with a break-up and disappearance of the internal elastic lamina such as we also find in the depths of an atheromatous plaque I think it possible that in this way the skeleton of the canalised thrombus may also receive a part of its blood-supply from the vasa vasorum (fig 5) and the rest from the canalised vessels Thus organisation and canalisation of a thrombus may coexist although the two circulations do not commingle This is simply a development of the

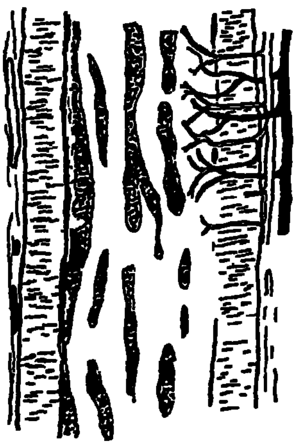

Fig 5—Hypothetical diagram of blood-supply from vasa vasorum to parts of framework of canalised thrombus

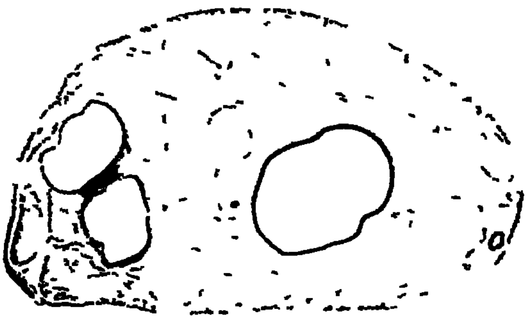

Fig 6—Dilated collateral arteries in sciatic nerve of man, aged 73, with senile atherosclerotic ischæmia (×9.5)

essential dual blood-supply of the arterial wall and appears to be its logical consequence.

Collateral Circulation

Where the arterial circulation is occluded, whether slowly or acutely, the blood tends to be diverted into other channels, known as collaterals. The collateral arteries are already formed vessels—so far as my investigations go, no new arteries are formed—and many of them are the named branches of the anatomists. Together they make up the arcade systems so characteristic of much of the arterial supply to the skin, muscles, and limbs. They are found in the subcutaneous tissues, in the intermuscular planes, on the periosteum, and in the nerve trunks, and I have produced evidence that the muscular vessels may play a part; indeed it seems possible that ischæmic claudication of the calf-muscles may be due to the bypassing of the functional muscular tissue, to enhance the blood-supply to the skin and subcutaneous tissues of the toes threatened with gangrene.

These collaterals, in fulfilling their function, dilate into thin-walled vessels. This surprised me when I first began to examine them, because I was obsessed with the idea, which I suppose many pathologists indulge, that hypertrophy of an artery meant thickening of its walls—a picture very familiar to us in hypertension. Now the condition of these thin-walled tubes is intriguing. It is not technically easy to compare them with similar vessels which are not acting as collaterals, but I have measured similar vessels in the normal and the enlarged states by utilising the arteries of the sciatic nerve (fig 6). From this it emerges that the circumference may be increased to as much as twelve times, but with this the thickness of the wall is reduced to half the normal size (fig 7). This leads to the interesting question of the change in the cells which make up the muscle wall. The great disproportion between circumference and thickness clearly rules out simple stretching. The nearest analogy is to the pregnant uterus. Kolliker (1853) states that, by the end of the sixth month, the length of the uterine muscle-cells increases from seven to eleven times, and their thickness from two to five times, with the result that they enlarge in all dimensions. It is generally accepted that they also increase in number. In the wall of the arteries which we are considering the condition is different because, though the vessel is dilated, its wall is thinned. But, since this thinning is less than it would be if the wall were merely stretched, either the cells must thicken or new cells must be added.

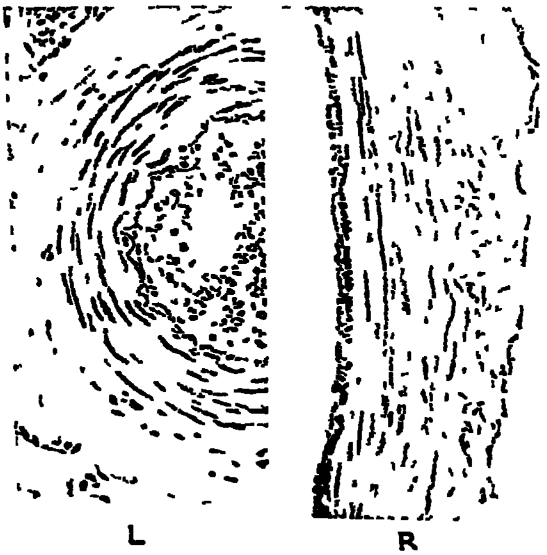

Fig 7—Normal sciatic (comites nervi) artery (L) compared with larger vessel in fig 6 at same magnification (R). Note relative thinning of muscular wall and of muscle nuclei in R (×150)

The number of cells in a cross-section of an artery may be estimated approximately by counting the nuclei, and in the case in point this shows some 500 cells in the section of the dilated artery compared to 200 in the corresponding control artery. What is the condition of the individual cells which causes the vessel to become thinner although their number is increased? If all the cells were to undergo the same change in size, and extra ones of the same size were simply packed in, the result could be cells twelve times the length and a fifth of the thickness of the normal. But this tremendous elongation seems unlikely, and it appears more reasonable to suppose that, like those of the uterus, they are perhaps six times the length but, unlike them, only about two-fifths of the normal thickness. This is very speculative because we do not know the extent to which they overlap each other. The exact change will have to be decided by maceration and dissection, but in any case the arterial muscle-cells must be much thinner in proportion to their length.

At this point I thought I might get some further information from the size of the nuclei, because the nuclei figured in enlarged uterine cells are definitely enlarged in all dimensions. Comparing the size of the muscle nuclei in different arteries I found (what I did not know before but might have deduced) that the size of the nucleus in these cells is related to the size of the artery. Large vessels have cells with large nuclei, and small vessels cells with small nuclei. I was therefore driven back to comparing sciatic arteries and found that the length of the nuclei in the cells I knew to be greatly elongated were not measurably greater than those in the control vessel. On the other hand, it was evident from inspection that they were decidedly thinner (fig 7), though the difference was difficult to measure. On taking mean figures and comparing the bulk of each nucleus, as the product of length and breadth, it appeared that the normal cell nucleus is about twice as bulky as the nucleus of the elongated cell. This rather surprising result seems to suggest that, in the maximally enlarged collateral, an element of atrophy may supervene.

It is obvious that the stimulus to this peculiar alteration in the arterial structure must be quite different from that which produces the thick-walled artery of hypertension. Wherein lies this difference? As regards hæmodynamics, there is an analogy with arteriovenous fistula, in which the artery discharging into the vein dilates, the reason seemingly being the lack of peripheral resistance, and the result an increased blood-flow Such factors may operate in the ischæmic limb For example, a terminal anterior branch of the peroneal artery normally inosculates with the anterior tibial and shares its tension at the point of junction But suppose, as often happens, the anterior tibial becomes occluded proximal to this anastomosis, the tension at and beyond the anastomosis is *immediately* reduced, such pressure as there is being maintained mainly by the flow of blood from the lateral plantar artery In chronic peripheral ischæmia from atherosclerosis the arteries of the foot are commonly patent and patulous, so such an occlusion as I have supposed would permit an excessive flow of blood from the peroneal branch into an area of abnormally low tension in the foot It is common for the posterior tibial artery also to be occluded, which would still further decrease the pressure in the vessels of the foot and favour an even greater flow of blood through the peroneal anastomosing branch, which would dilate to pass the amount of blood normally transmitted by these two larger channels as well as its own normal contribution

It therefore seems that an artery in a position to transmit blood against a lowered peripheral resistance will *dilate*, whereas one transmitting blood against an increased peripheral resistance will thicken

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MODE OF ACTION OF
ORAL ANTIDIABETIC COMPOUNDS

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IN the three years that have elapsed since the publication of the first papers on carbutamide (Achelis and Hardebeck 1955, Bertram et al 1955, Franke and Fuchs 1955) many clinical observations and experimental results have been published dealing with various possibilities of site and mechanism of the hypoglycæmic effect of this compound and other " oral antidiabetic drugs "

We describe here the situation as we see it today, emphasising beforehand that a full understanding of the details of this mechanism has, of course, not been obtained—not even a high degree of certainty about its broad outline

Action on or via Endocrine Glands

In the treatment of diabetes mellitus the effect of the oral antidiabetic drugs is similar, in many ways, to that of giving small doses of insulin There is not, however, sufficient evidence that these drugs provoke an increase in the production and delivery of insulin from the cells of the pancreatic islets

In experiments on animals conflicting results have obtained from the study of islet-cell volume (Ashwor and Haist 1956, Kinash 1957) as well as from investigatio of the hypoglycæmic effect of small amounts of an diabetic compounds injected directly into the pancreatic duodenal artery (Loubatières 1946, Colwell et al 195 Houssay et al 1957a and b)

Pozza et al (1956) made cross-circulation experimen with carbutamide in eight pairs of dogs The blood sugar level fell in the recipient dogs, which receive blood from the pancreatic vein of the carbutamide treated donor dog, the blood-sugar level did not fall dogs connected to the mesenteric vein of donor dog However, only average figures of changes in blood-sug levels are given, and this kind of experiment does no seem to have been repeated by other workers

Some workers have described slight and inconstan changes in the staining reactions of the beta cells animals given oral antidiabetic compounds (Loubatière 1955, Kracht and Rausch-Stroomann 1956), but in th rat, at any rate, we feel convinced that no change take place in either the shape or the granulation of the insulin producing cells (Lundbæk and Nielsen 1958) (see table)

Another kind of " insulin action " was envisaged b Mirsky, who reported that the oral antidiabetic com pounds decreased the activity of insulinase in the liver of rats (Mirsky et al 1956, 1957) Evidently a decreas in the activity of an insulin-splitting enzyme would b equivalent to an increase in the activity of circulatin endogenous insulin In concentrations comparable t those eliciting a fall of the blood-sugar level this effect o insulinase activity was, however, very slight and perhap even dubious, and other workers have been unable t confirm Mirsky's hypothesis (Williams and Tucker 1956 Vaughan 1956, Cox et al 1956, Williams 1957)

The breakdown of insulin has also been studied with radioactive insulin Tolbutamide did not prolong th half-life of injected insulin labelled with ^{131}I (Wick et al 1957, Berson et al 1957, Volk et al 1957)

Even if neither the production nor the amount o circulating insulin were increased by the oral antidiabetic drugs, insulin action might still be enhanced by inhibition of one of the anti-insulin hormones Such a mechanism was one of the first to be proposed to explain the hypoglycæmic effect of these compounds Several investigators reported that 2-(*p*-aminobenzene-sulphamido)-5-isopropyl-thiodiazole (I P T D), carbutamide, and tolbutamide severely damaged the pancreatic alpha cells, thought to be the most important source of glucagon (von Holt et al 1956, Ferner and Runge 1956) Other workers found no damage to the alpha cells after administration of sulphonylureas (Volk et al 1956, Goldner et al 1957),

HISTOLOGICAL CHANGES IN PANCREATIC ALPHA AND BETA CELLS OF RATS AFTER ADMINISTRATION OF VARIOUS ANTIDIABETIC DRUGS
(From Lundbæk and Nielsen 1958)

Drug	No of animals	No of controls	Total dose (mg)	Histological changes of	
				Alpha cells	Beta cells
Carbutamide	75	29	75–3375	0	0
Tolbutamide	44	11	,,	0	0
I P T D	28	9		0	0
Synthalin A	10	3	20	+ → +	0
Total	*157*	52	—	—	—

nd our experiments with short- and long-term administration of large and small amounts of carbutamide, olbutamide, and IPTD in rats were completely negative Lundbæk and Nielsen 1958) (see table)

A hypoglycæmic effect due to depression of other antinsulin hormones seems to be excluded by the fact that he antidiabetic compounds are equally active or even nore active in animals deprived of the hypophysis, the drenal glands, the thyroid gland, the parathyroid glands, r the gonads (Loubatieres 1955, Houssay and Penhos 956, Lang and Sherry 1956)

Finally, if the hypoglycæmic action of the antidiabetic ompounds were an "insulin-like" effect—directly or indirectly—it would be expected to be accompanied regularly by hypophosphatæmia It has been reported that, in healthy people, intravenous tolbutamide decreases the amount of inorganic phosphate in the serum (Goetz et al 1956, Frawley et al 1957), but no change in the phosphate curve was found in diabetics in whom treatment with carbutamide or with tolbutamide significantly increased the tolerance of intravenous glucose, calculated on the blood-sugar values observed or on the "excess blood sugar" (Eskjær Jensen et al 1958) (fig 1)

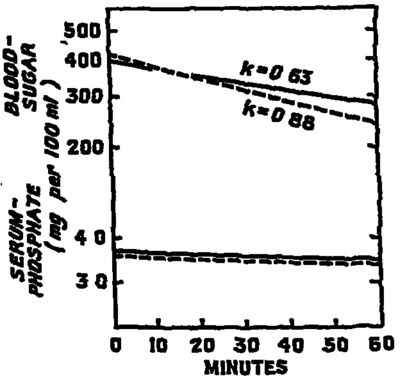

Fig 1—Average curves of intravenous glucose-tolerance tests and serum inorganic phosphate before (continuous line) and during (interrupted line) treatment with antidiabetic drug (Eskjær Jensen et al 1958)

On the whole it seems to us that, at present, the hypoglycæmic effect of the oral antidiabetic drugs has not been shown to be due either to augmentation of insulin action or to inhibition of the actino of the antidiabetic hormones

Site of Action

Intestines

In rats given large doses of carbutamide orally in short-time experiments Friedlich et al (1956) found a decreased intestinal absorption of glucose In human beings treated with tolbutamide there is no such effect (Frawley et al 1957), and it is well known that the antidiabetic compounds are very active when given intravenously

Liver

Several workers have found that the oral antidiabetic compounds influence the output of glucose from the liver Anderson et al (1956, 1957), who catheterised the hepatic vein in tolbutamide-treated dogs, observed a pronounced inhibition of the release of glucose from the liver This finding was confirmed by Schambye and Tarding (1957), and Kibler and Gordon (1956) observed the same phenomenon in diabetic patients

A hepatic effect is also obvious from the fact that the administration of oral antidiabetic compounds increases the amount of glycogen in the liver (Bänder and Scholz 1956, Tyberghein et al 1956, Miller and Dulin 1956)

The action on the liver has been studied further in vitro The production of glucose in liver slices has been reported to be reduced in the presence of antidiabetic compounds (Clarke et al 1956, Frawley et al 1957), but other workers have found either no decrease or a decrease only at excessively high concentrations (Ashmore et al 1956, 1957, Berthet et al 1956) Glucose-6-phosphatase activity is inhibited by carbutamide and tolbutamide, but also only in very high concentrations (Ashmore et al 1956, 1957, Tyberghein et al 1956, Hawkins et al 1956, Haist et al 1957, Berthet et al 1956, Kuether et al 1956, 1957)

It thus seems that, although the precise mode of action in the liver has not yet been elucidated, the inhibitory action of these compounds on the output of glucose from the liver may be accepted On the other hand, it is now known that the presence of the liver is no prerequisite for the hypoglycæmic effect of the oral antidiabetic compounds A fall of the blood-sugar level is seen in hepatectomised animals given tolbutamide or N'-β-phenethylformamidinyliminourea (Phenethyl-diguanide, DBI) (Dulin and Johnston 1957, Williams et al 1957)

At the Periphery

The possibility of an action on the uptake of glucose at the periphery, has been less intensely explored, probably because some of the earlier studies were regarded as rather definitive proofs against such a mechanism

In perfusion experiments with eviscerated animals no effect of carbutamide or of tolbutamide was found by Lang and Sherry (1956), Fritz et al (1956), and Wick et al (1956) Investigations of the arteriovenous blood-sugar difference after the administration of antidiabetic drugs in man have given conflicting results (Goetz et al 1956, Recant and Fischer 1957)

The Gemmill method, by which the uptake of glucose and the synthesis of glycogen in the isolated rat diaphragm are determined in vitro, should be a useful tool for elucidating this problem Clarke et al (1956), Cahill et al (1957), and Recant and Fischer (1957) reported that carbutamide and tolbutamide had no effect on the uptake of glucose from the medium, but DBI increases the uptake of glucose by the rat diaphragm (Williams et al 1957)

In our laboratory a clearly increased uptake of glucose was found with carbutamide as well as with tolbutamide and IPTD, also in concentrations comparable to the levels achieved in the blood when these drugs are used in patients (Rafaelsen 1958) (fig 2) We have also confirmed the finding of Williams et al (1957) that DBI has a strong effect on the uptake of glucose (fig 2) The reason for the failure of earlier workers to observe the relatively mild effect of carbutamide and of tolbutamide on the uptake of glucose by isolated muscle is not quite clear Most studies have, however, included only few experiments, and in the largest one (Recant and Fischer 1957) the standard deviation of the result is surprisingly high

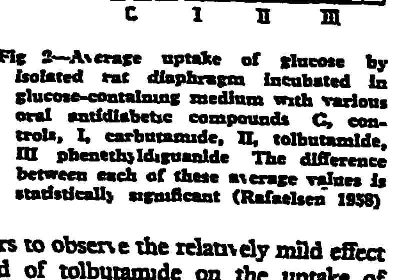

Fig 2—Average uptake of glucose by isolated rat diaphragm incubated in glucose-containing medium with various oral antidiabetic compounds C, controls, I, carbutamide, II, tolbutamide, III phenethyldiguanide The difference between each of these average values is statistically significant (Rafaelsen 1958)

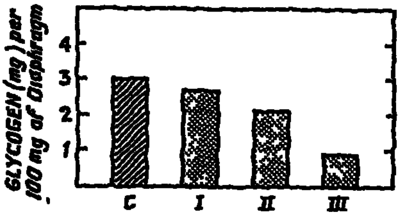

Fig 3—Average glycogen content of isolated rat diaphragm after incubation in glucose-containing medium with various oral antidiabetic compounds C, I, II, and III as in fig 3 III is significantly lower than C, I, and II (Rafaelsen 1958)

The amount of glycogen in muscle is not increased either by carbutamide or by tolbutamide (Rafaelsen 1958), it is even decreased by D B I (Williams et al 1957, Rafaelsen 1958) (fig 3) This finding suggests that the effect of the antidiabetic compounds on the carbohydrate *metabolism of muscle differs from that of insulin*, which in concentrations above 10^{-3} I U per ml always induces the accumulation of glycogen in the isolated rat diaphragm

On the other hand, we have found that these drugs influence the uptake of galactose and fructose without affecting that of *d*-arabinose, just as insulin does (fig 4)

The details of the mechanism of this peripheral action on muscle are under investigation at present—especially the question whether it works by either of the two pathways of glucose metabolism in muscle recently described by Shaw and Stadie (1957)

Experiments in which the effect of oral antidiabetic compounds on the formation of $^{14}CO_2$ from glucose labelled with ^{14}C was estimated have been published by several laboratories Wick et al (1956) and Williams et al (1957) found no demonstrable effect, but Miller et al (1957) and Rice (1957) reported a rather pronounced increase in the combustion of glucose, measured by this technique

It therefore seems that enhancement of the uptake of glucose at the periphery is one of the modes of action of the oral antidiabetic drugs Both the hypoglycæmia following the *administration* of these compounds in hepatectomised animals and the result obtained with isolated muscle point in this direction

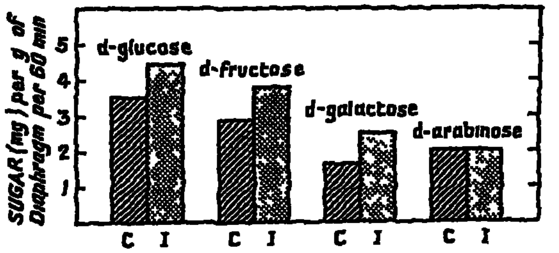

Fig 4—Average uptake of various sugars by isolated rat diaphragm incubated in media containing these sugars and carbutamide C and I as in fig 3 Increased uptake of *d*-glucose, *d*-fructose, and *d*-galactose due to carbutamide are statistically significant (Rafaelsen 1958)

Prerequisites for Hypoglycæmic Effect of Antidiabetic Drugs

The German workers who introduced carbutamide noted that it had no effect, or only a very slight effect, on patients with severe diabetes mellitus (Franke and Fuchs 1955, Bertram et al 1955) Most workers have found that I P T D, carbutamide, and tolbutamide are without effect in animals with severe alloxan diabetes (Loubatières 1946, Achelis and Hardebeck 1955, Lang and Sherry 1956, Bänder and Scholz 1956)

Mirsky et al (1957) compared the hypoglycæmic effect of tolbutamide on alloxanised rabbits with various degrees of hyperglycæmia In rabbits with only mild hyperglycæmia an antidiabetic effect could be obtained, but rabbits with very high blood-sugar levels did not respond

Other workers have emphasised that the action of insulin seems to be potentiated by antidiabetic drugs when carbutamide or tolbutamide is given to pancreatectomised dogs receiving constant amounts of insulin, the blood-sugar level is lowered further (Sirek and Sirek 1956, Houssay et al 1957, Ricketts et al 1957)

These clinical observations and experimental results have been regarded by many workers as evidence that the presence of insulin, either from functioning beta cells or as administered insulin, is a prerequisite for the hypoglycæmic action of these compounds

D B I, the latest oral antidiabetic drug to be discovered, does, however, produce hypoglycæmia in young patients with severe diabetes mellitus and in animals with severe alloxan diabetes (Williams et al 1957), and in our preliminary in-vitro experiments with diaphragms of alloxanised rats a statistically significant increase in the uptake of glucose was found even with carbutamide (Lundbæk and Rafaelsen 1958)

Finally, a clearcut fall of the blood-sugar level can be obtained in the hypophysectomised pancreatectomised dog (Houssay et al 1957a and b) Such dogs have no source of insulin, but their blood-sugar level is close to normal

Perhaps the results obtained in different degrees of severity of clinical diabetes mellitus and of experimental diabetes in animals should be formulated not in terms of the presence or the absence of insulin in the organism but in terms of the degree of severity of the diabetes It seems that the milder of the compounds—carbutamide and tolbutamide—act on carbohydrate metabolism to produce demonstrable effects when, and only when, the endocrine balance is normal or rather close to normal, not when a profound state of disequilibrium obtains D B I has a stronger effect and can normalise a more pronounced diabetic aberration of metabolism

Summary

On present evidence the hypoglycæmic effect of the oral antidiabetic drugs cannot be explained by interference with the endocrine balance of the organism

Among the modes of action of these compounds inhibition of the output of glucose by the liver and enhancement of the uptake of glucose at the periphery seem to be acceptable The detail of the changes in enzyme activities probably involved in the hepatic and peripheral effects have not been elucidated

It is suggested that the hypoglycæmic effect of the oral antidiabetic compounds is determined not by the presence or absence of insulin but by the degree of diabetic aberration of metabolism

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HEINZ-BODY ANÆMIA DUE TO SALICYLAZOSULPHAPYRIDINE

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SALICYLAZOSULPHAPYRIDINE was introduced by Svartz (1942) for treating ulcerative colitis Taken by mouth it is absorbed from the gut and is deposited in connective tissue, including that in the bowel, where aminosalicylic acid and sulphapyridine are gradually liberated Free sulphapyridine can be detected in the blood

It has been extensively used in the Scandinavian countries (Svartz 1948, 1954, 1956, Lagercrantz 1949, 1955), and has been used in America under the names of 'Azopyrin' and 'Asulfidine' (Morrison 1952, 1953) Bargen (1955), who has a very large experience of ulcerative colitis, states that "the most valuable drug that has been introduced for the treatment of ulcerative colitis in the years that I have been interested in the problem is salicylazosulfapyridine"

In this country the drug has been available only for the past three years, under the name 'Salazopyrin' Since it seems possible that its use will increase, it is necessary to be aware of its toxic effects Nausea or vomiting develops in 1 patient in about 5 or 6 treated with salazopyrin Less common are skin rashes, drug fever, and joint reactions Serious toxic reactions are said to be rare, the principal one being neutropenia going on to agranulocytosis

After seeing 2 patients (cases 1 and 2 below) in whom toxic anæmia with Heinz-body formation developed during salazopyrin therapy, we began to make regular examinations for Heinz bodies in all patients receiving the drug, and a further case has since been discovered (case 3)

Technical Methods

Demonstration of Heinz Bodies

Method I (wet preparation).—A few drops of blood from a finger-prick are taken into about double their volume of 0·5% methyl-violet in isotonic saline solution (The stain solution must be filtered before use.) After the blood has stood for a few minutes, a drop of it is examined under a cover-slip with the oil-immersion objective

Method II (permanent preparation).—A few drops of blood from a finger-prick are taken into isotonic saline solution containing 0 5% sodium citrate. The tube is centrifuged until the cells are deposited, and the supernatant fluid is poured off The red cells are resuspended in isotonic saline solution containing 0·5% methyl-violet (This solution must be filtered immediately before use.) The tube is centrifuged again, and films are made from the deposited red cells with the least possible delay These are air-dried and mounted without any counterstain

By either of the above methods Heinz bodies are shown as darkly stained discrete particles in the almost colourless red cells

Reticulum is visible as a diffuse violet mottling or speckling

Other Methods

All other hæmatological techniques used were those recommended by Dacie (1956)

Case-reports

Case 1.—A man, aged 28, was put on salazopyrin therapy on Aug 23, 1956, for severe ulcerative colitis He had a past

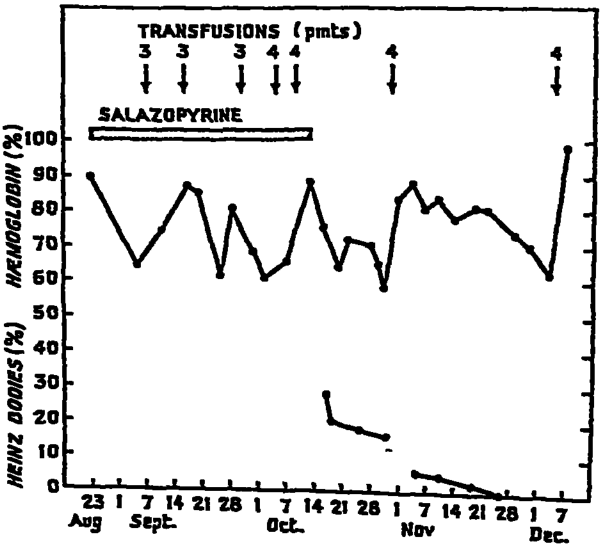

Fig 1—Treatment and course in case 1

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TABLE I—MAIN HÆMATOLOGICAL DATA IN CASE I

Date	Hæmoglobin (%)	Hæmoglobin (g per 100 ml)	Reticulocytes (%)	Heinz bodies (%)	White cells (per c mm)	Blood transfused (pints)	Other investigations
Aug 2, 1956	96	14 2			5600		
Sept 4, „	65	9 6					Film anisocytosis, hypochromia, occasional normoblasts
„ 5, „						3	
„ 10, „	75	11 1			9500		
„ 15, „						3	
„ 17, „	87	12 9					
„ 22, „	63	9 3					Film anisocytosis, hypochromia, polychromasia
„ 26, „						3	
„ 27, „	82	12 1					
Oct 3, „	61	9 0	9 6				Film anisocytosis, polychromasia, some spherocytes and fragmented cells, Coombs test negative, osmotic fragility normal
„ 5, „						4	
„ 9, „	65	9 6	5 0				
„ 10, „						4	
„ 11, „	90	13 3					
„ 15, „	76	11 2		28 8			
„ 17, „	64	9 5	2 4	20 6			
„ 24, „	70	10 4	4 0	17 6			
„ 30, „	58	8 6	3 2	15 8	7700		Film very few spherocytes or fragmented cells
„ 31, „						4	
Nov 6, „	88	13 0	5 2	4 6			
„ 12, „	82	12 1	3 6	4 2			Film moderate polychromasia only
„ 20, „	80	11 8		2 8			
„ 27, „	73	10 8	4 0	Very few			
Dec 4, „	63	9 3	6 0	None			
„ 6, „						4	
„ 7, „	98	14 5	6 0		8500		Film moderate polychromasia
„ 21, „	95	14 1		None			
May 3, 1957	105	15 5					Film normal

history of tuberculosis, beginning with a pleural effusion in May, 1949, and ending with antituberculous treatment in 1951 and 1952 for caries of the spine His first episode of diarrhœa was in January, 1956, lasting only three days, and further episodes occurred in March and in May of the same year From June, 1956, he had continuous abdominal discomfort and increasingly loose bloodstained motions containing mucus An inflamed and ulcerated mucosa was seen on sigmoidoscopy By August, 1956, he was having upwards of twenty-five motions daily and required repeated transfusions to maintain his hæmoglobin

Salazopyrin therapy was begun on Aug 23, 1956 The initial dose of 2 0 g q d s was reduced after five days to 1 0 g q d s At the same time the patient was given corticotrophin gel 80 units daily for twenty-one days, followed by 40 units daily for twenty-one days, and (because of the history of tuberculosis) intramuscular streptomycin 0 5 g b d

Hæmatology —After ten days the patient became less ill and during the next month the diarrhœa was considerably improved and obvious blood ceased to be present in the stools, but increasingly frequent blood-transfusions were needed to maintain a satisfactory level of hæmoglobin (fig 1) On Oct 3, 1956, and again on Oct 9, 1956, spherocytes and fragmented red cells were seen in blood-films, and the reticulocytes were 9 6% and 5 0%, red-cell fragility and plasma-bilirubin were normal The Coombs test was negative, and there was no methæmoglobinæmia On Oct 13, 1956, the salazopyrin was discontinued because it was thought to be responsible for the anæmia Heinz bodies were first looked for on Oct 15, 1956, and were found in 30% of the red cells Over the next four weeks the percentage of affected red cells diminished steadily and they finally disappeared (fig 1) The fragmented cells also disappeared, and only two more blood-transfusions were necessary before the patient was discharged from hospital. When last seen the patient was at full work, with hæmoglobin 105%, and symptom-free

The main hæmatological data are set out in table I

Case 2 —A woman aged 65, was treated with salazopyrin for a malabsorption syndrome due to an ileocolic fistula After having a perforated appendix in 1936 she had several operations for intestinal obstruction, including an anastomosis and a resection of a segment of bowel In 1942 she began to have diarrhœa with loose bulky offensive stools From 1947 onwards she was treated for macrocytic anæmia and steatorrhœa

Salazopyrin therapy —In November, 1956, the patient was readmitted under Prof G W Pickering Barium studies showed an ileocolic fistula, and, to reduce bacterial colonisation of the small intestine, salazopyrin was given in a dosage of 2 g t d s , beginning on Dec 2, 1956

Hæmatology —Before salazopyrin was given the patient had a normal blood picture On Dec 17, 1956, her hæmoglobin level was 78%, and the reticulocyte-count was 4 5% The reticulocyte preparation showed large inclusion bodies in 95% of the red cells, and these were shown to be Heinz bodies (fig 2 shows the appearance next day) A blood film showed much fragmentation and distortion of the red cells The plasma-bilirubin level was 0 9 mg per 100 ml , and a little methæmoglobin was found The fragility of the red cells was normal, and a direct Coombs test was negative

Salazopyrin was immediately discontinued The hæmoglobin level, which had fallen to 58% by Dec 19, 1956, began to rise spontaneously, while the Heinz bodies showed a steady fall (fig 3) Five weeks after the salazopyrin had been discontinued the blood-picture was normal

The main hæmatological data are given in table II

Case 3 —A man, aged 61, was given salazopyrin for ulcerative colitis On starting medical treatment he was having twenty-five motions daily and had pyrexia and tachycardia

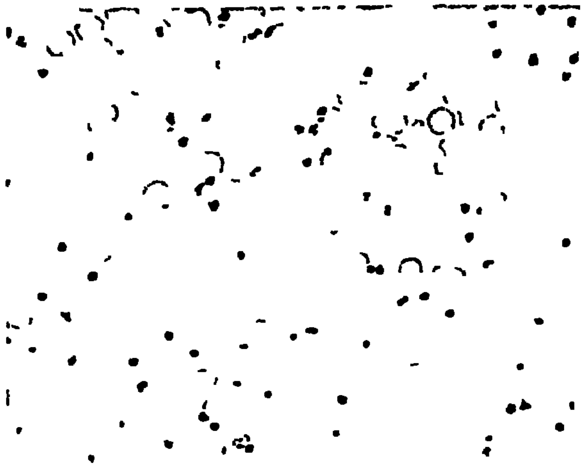

Fig 2—Blood of case 2 stained supravitally for Heinz bodies

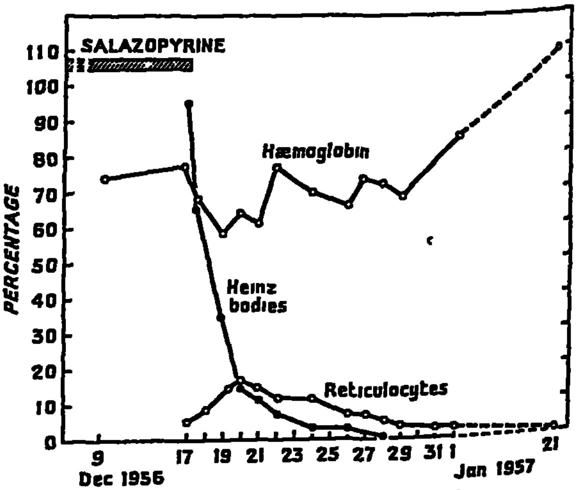

Fig 3—Treatment and course in case 2.

TABLE II—MAIN HÆMATOLOGICAL DATA IN CASE 2

Date	Hæmoglobin (%)	Hæmoglobin (g per 100 ml)	Reticulocytes (%)	Heinz bodies (%)	White cells (per c mm)	Other investigations
Nov 26, 1956	90	13·3			6500	Film normal
Dec. 9, "	76	11·2				
" 17, "	78	11·5	4·5	95		
" 18, "	67	9·9	9·4	65		Film much fragmentation, plasma-bilirubin 0·9 mg per 100 ml., methæmoglobin present, osmotic fragility normal, Coombs test negative
" 19, "	58	8·6	15·4	30		
" 20, "	64	9·5	16·2	16	6250	
" 21, "	61	9·0	14·5	11		Film moderate fragmentation, much polychromasia
22, "	77	11·4	12·8	7		
" 24, "	70	10·4	11·1	3·6		
" 26, "	67	9·9	7·7	1·9		
" 27, "	73	10·8	8·1	1·0		
" 28, "	72	10·7	5·6	0·6		Film very few fragmented cells, slight polychromasia
" 29 "	69	10·2	3·6	Very few		
" 31, "	87	12·9	2·6	Very few		
Jan. 1, 1957	81	12·0	2·1	None		
" 21, "	108	16·0	Very few	None	3800	Film normal
July 5, "	96	14·2		None	5000	Film normal

Under treatment with intramuscular corticotrophin gel 80 units daily and blood-transfusions the diarrhœa lessened and the stools no longer contained obvious blood On Feb 22, 1957 corticotrophin was withheld and the patient was put on to salazopyrin 1·0 g q d s He required a blood-transfusion of 4 pints on Feb 26, and again on March 12, 1957, and March 22, 1957

Heinz bodies were first found on March 25, 1957, and were present in 26% of the red cells Salazopyrin was immediately discontinued, and thereafter the percentage of cells containing Heinz bodies decreased steadily, reaching very low levels in a fortnight No further transfusions were necessary On discharge from hospital the patient was symptom-free

The main hæmatological data are set out in table III

Discussion

With few exceptions the presence of large numbers of Heinz bodies points to chemical poisoning Among numerous toxic substances which cause Heinz bodies to form are benzene derivatives with amino- or nitro-groups such as phenylhydrazine, phenacetin, and the sulphonamides (Fertman and Fertman 1955) In the last group sulphanilamide and sulphapyridine are particularly active. Probably many of the cases of anæmia reported as being due to sulphonamides (Wood 1938) were of this type, but until the publications of Moeschlin (1940, 1941) the characteristic inclusion bodies were not sought for

TABLE III—MAIN HÆMATOLOGICAL DATA IN CASE 3

Date	Hæmoglobin (%)	Hæmoglobin (g per 100 ml)	Reticulocytes (%)	Heinz bodies (%)	Blood transfused (pints)	Other investigations
Feb 19, 1957	75	11·1				Film hypochromia, polychromasia
" 26 "					4	
March 11 "	63	9·3		None		
" 12, "					4	
" 18, "	7	11·4				
" 22, "					4	
25, "	100	14·8		26		Film much fragmentation, some spherocytes
" 26 "	89	13·2	2·4	20·3		
" 27 "	93	13·8		18·3		
28, "	88	13·0	3·2	14·6		
29 "	88	13·0		17·3		
" 30 "	90	13·3		4·6		
April 1 "	86	12·7	2·4	3·3		
" 2	90	13·3				
3	8	12·9	2·0	9·3		
" 6, "	83	12·3		6·0		
" 8, "	7	11·4	1·2	Very few		
" 16 "	85	12·6	2·0	Very few		
June 14	102	15·1		None		Film normal
July 12, "	101	14·9				

In the present three cases salazopyrin was the only drug used which forms Heinz bodies Withdrawal of the salazopyrin was followed by an immediate fall in the Heinz-body count and an arrest of the hæmolytic anæmia It therefore seems certain that the anæmia was due to salazopyrin intoxication.

The hæmolytic anæmia associated with Heinz bodies is principally determined by the diminished life-span of the affected red cells Reported figures for the rate of disappearance of Heinz bodies after cessation of drug treatment lie between four days (Markoff 1943) and thirty days (Gasser 1953) The Heinz bodies in the three present cases had disappeared after forty-nine, eleven, and fourteen days Possibly the Heinz bodies may be extruded during the life of the red cell, if not, the shape of the disappearance curves indicates either that the affected cells are randomly destroyed or that different cells in the same sample have very different life-spans according to number of Heinz bodies

The anæmia is probably aggravated by the degradation of hæmoglobin in the affected red cells Chemical studies and electron-microscopy have shown that Heinz bodies are very dense and contain a large amount of iron (Rozsa and Spicer 1953), and it is generally agreed that they are derived from hæmoglobin The facts that they can be produced in red blood-cells by numerous chemical agents in vitro and that they are seldom, if ever, found in reticulocytes or in nucleated red cells indicate that the inclusions are formed in vivo in the circulating mature red cells Methæmoglobinæmia and other abnormal pigments sometimes occur in these anæmias (Dacie 1954), and methæmoglobin was found in case 2

In view of our experience with these cases we have made it a routine to examine the blood for Heinz bodies in all patients receiving salazopyrin Since Heinz bodies are invisible in Romanowsky-stained blood-films, it is essential that they should be looked for specially Hæmolytic anæmia is easily overlooked in a patient with ulcerative colitis who is losing blood If such a patient is being treated with salazopyrin, the special examination for Heinz bodies provides an easy means of showing when the anæmia is due not to the disease but to the treatment.

Summary

Three cases of Heinz-body anæmia due to the use of salicylazosulphapyridine (' Salazopyrin ') are reported

The blood of patients treated with salazopyrin and other sulphonamides should be regularly examined for Heinz bodies

We are grateful to Dr A H T Robb-Smith, Dr R G Macfarlane, and Prof L J Witts for helpful criticism and to Prof Sir George Pickering for permission to include case 2

ADDENDUM

Since this article was written, another case of Heinz-body anæmia has occurred in a patient receiving salicylazosulphapyridine We have now made regular observations on 32 patients with ulcerative colitis being treated with this drug, so that this case, together with case 3, shows that the complication is fairly common

References overleaf

SERUM-PROTEINS IN PATIENTS WITH NON-HÆMOLYTIC TRANSFUSION REACTIONS

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Though *there are more and more blood-transfusions*, hæmolytic reactions are rare, because they are eliminated by adequate compatibility tests, and the perils of contamination are practically excluded by expert preparation and handling of the blood and instruments On the other hand, troubles are cropping up which we cannot explain in spite of all precautions some patients react unfavourably to transfusions which are correctly administered These troubles may arise during or shortly after the transfusion Most frequently they present with symptoms of fever and allergy—shivering, laboured breathing, cyanosis, low blood-pressure, rashes, and sometimes shock Such conditions are always distressing and may be dangerous

Symptoms of this kind are seen chiefly in exhausted patients with hypoproteinæmia or with dysproteinæmia

MEAN LEVELS OF TOTAL PROTEIN AND OF ELECTROPHORETIC FRACTIONS IN SERUM (G PER 100 ML)

Group	No of persons	Total protein	Albumin	Globulin				A/G ratio
				α_1	α_2	β	γ	
Healthy donors	18	7 14	4 02	0 42	0 56	0 79	1 36	1 29
Non-reactors	34	7 2	3 46	0 36	0 77	0 74	1 89	1 00
Reactors	24	6 2	2 72	0 36	0 67	0 75	1 73	0 88

Such patients can usually be given safely either blood partially freed from plasma, or (better still), washed erythrocytes suspended in saline solution Dameshek and Neber (1950) described transfusion reactions caused by some constituents of plasma, and Crosby and Stefanini (1952) published similar cases Possibly, therefore, non-hæmolytic reactions might be induced by the composition of the patient's plasma and/or by that of the transfused blood

So far no reliable method has been developed by which we can investigate the compatibility of plasma-proteins as a routine in the same way as we test the compatibility of the patient's and donor's plasma and erythrocytes We take blood for transfusion from "healthy donors" without knowing much about the composition of their plasma-proteins We still use these proteins in transfusions as we formerly used the erythrocytes of "universal donors," assuming that the composition of the donor's plasma is almost always constant On the other hand, we know that the recipient's plasma is very often abnormal, and methods in current use make it possible to establish important individual differences in the plasma-proteins of our patients

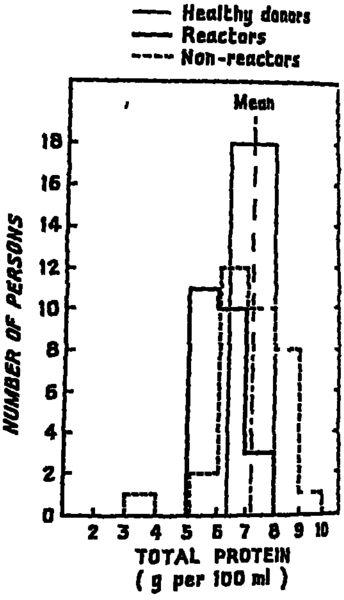

Fig 1—Distribution of levels of total proteins in serum

We accordingly investigated the serum-proteins of patients who had had non-hæmolytic reactions to transfusion We tried to discover (1) whether there were significant differences between the serum-proteins of patients who had reacted and those who had not, (2) whether examination of the serum-proteins of a patient could indicate hypersensitivity to whole blood, and (3) whether such reactions could be avoided by transfusing sensitive patients with blood partially or totally freed from plasma

Materials and Methods

At our request, hospitals sent us samples of fresh blood from every patient who had reacted unfavourably to a blood-transfusion, as well as from many patients who had not so reacted, together with all available information about the diagnosis, clinical course, and previous blood-transfusions Serum was taken from these samples and analysed the same morning All samples which came from patients who had had hæmolytic reactions to transfusion, and all hæmolytic sera, were discarded

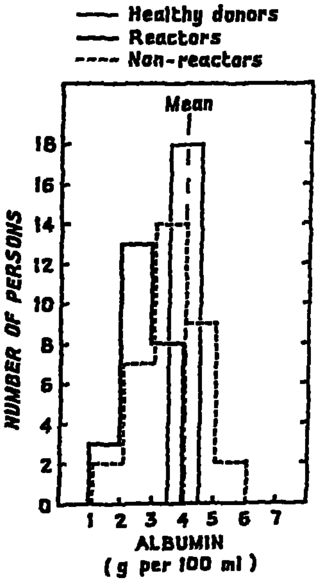

Fig 2—Distribution of serum-albumin levels

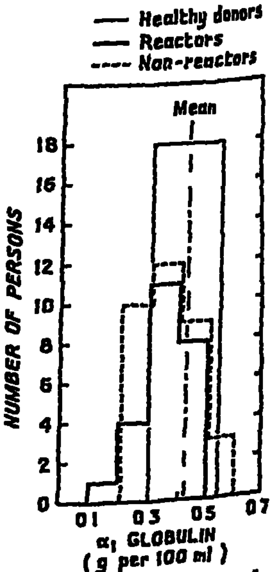

Fig 3—Distribution of α_1-globulin levels in serum

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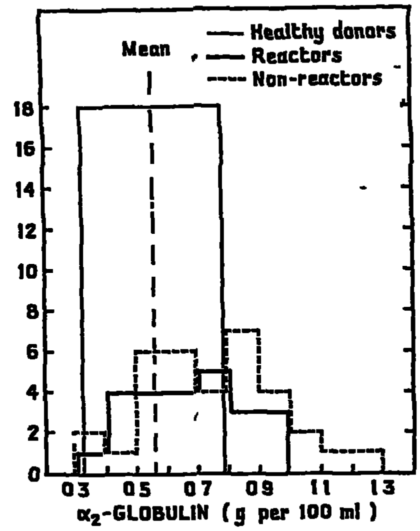

Fig 4—Distribution of α_2-globulin levels in serum

Laboratory analysis consisted in determination of total protein by the biuret method of Wolfson et al (1948) and of paper electrophoresis carried out horizontally in a closed chamber in M/20 phosphate buffer pH 8 9 The dried strips were stained with bromophenol blue and percentages of fractions estimated by cutting out, elution, and photometry These values were converted into absolute concentrations by multiplication by the factor for total protein

This procedure was applied to the sera of a random group of healthy blood-donors, a random group of recipients of blood-transfusions who had had no symptoms of reaction, and all those patients whose unfavourable reaction to blood-transfusions could not be ascribed either to faulty matching of blood-groups or factors or to contamination

Results

The mean levels of total protein and electrophoretic fractions in the serum of healthy donors, patients who had no reactions, and those who had non-hæmolytic reactions are shown in the accompanying table and their distribution in figs 1–6

It is evident that, in our groups, non-hæmolytic reactions to blood-transfusions were commoner in patients who had low serum-protein levels, especially low serum-albumin levels As regards β-globulins, we found no significant difference between recipients who reacted and those who did not α_2-globulin levels were more often raised in non-reactors than in reactors, whereas α_1-globulin levels were more often subnormal in non-reactors than in reactors

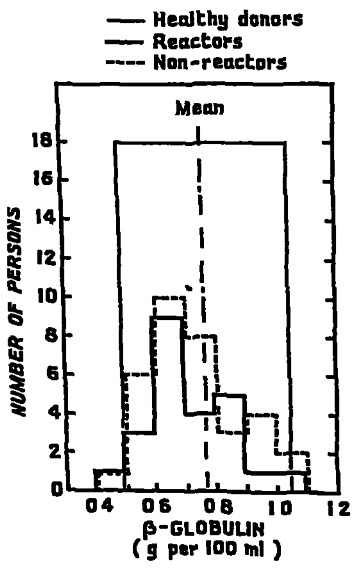

Fig 5—Distribution of β-globulin levels in serum

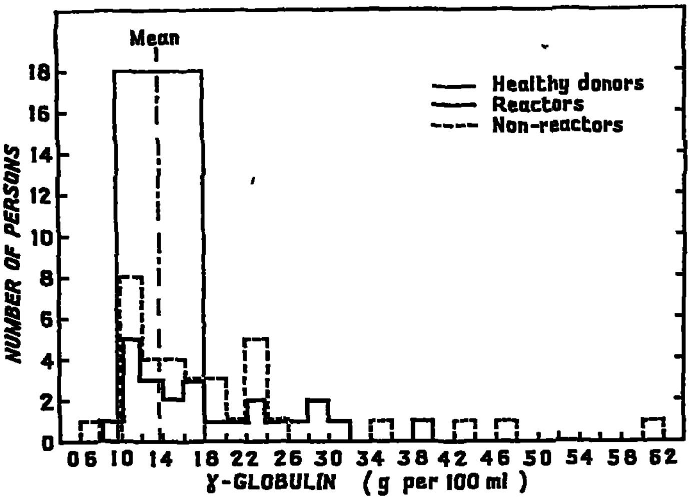

Fig 6—Distribution of γ-globulin levels in serum

In both groups some patients had hypergammaglobulinæmia, but, in our experience, hypergammaglobulinæmia does not contribute to the development of transfusion reactions On the contrary, patients with extreme hypergammaglobulinæmia (2 with kala-azar, 1 with leukæmia, 1 undiagnosed) took blood-transfusions very well

The albumin/globulin ratio in the serum was in many patients lower than normal, the means (see table) were below normal in both groups of recipients, being lower in the reactors than in the non-reactors In most cases the low ratio was not due to hyperglobulinæmia but to hypoalbuminæmia

Conclusions

It seems to us, that, when transfusion is not very urgent, it might be useful to analyse the patient's serum-proteins Several patients who reacted unfavourably to whole blood took washed erythrocytes very well These patients had low serum-protein levels, especially a low serum-albumin Patients with such abnormalities in plasma-proteins should be given blood practically free from plasma Such blood should always be given to patients who have had a non-hæmolytic reaction to a previous blood-transfusion

Washed erythrocytes, of course, have not the biological value of whole blood, they can still be useful to a weakened organism By giving them one can spare the recipient's plasma-proteins, which are used for synthesising hæmoglobin (Whipple 1948)

We claim that this treatment is more physiological than the routine use of antiallergic and other drugs to prevent transfusion reactions

When we had almost completed our investigation, we found that Wigand (1957), Moller (1957), and Kryger (1957) had also found that non-hæmolytic reactions to blood-transfusion were commoner in patients with abnormal serum-protein levels

Summary

The serum levels of total protein and electrophoretic protein fractions were estimated (a) in patients who had had (non-hæmolytic) reactions to blood-transfusion, (2) in healthy blood-donors, and (3) in patients who had taken blood-transfusion well

Subnormal total-protein levels—and especially a low serum-albumin—were found most often in the patients who had reacted badly to blood-transfusion

It is recommended that, in non-urgent cases the patient's serum-proteins should be determined before transfusion

Where the serum-protein, and especially the serum-albumin, is low, the patient should be given washed erythrocytes instead of whole blood

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TOTAL GASTRECTOMY FOR BENIGN PEPTIC ULCER

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TOTAL gastrectomy is rightly regarded as a serious undertaking and is usually reserved for treating carcinoma of the stomach Balint et al (1957) suggest, however, that total gastrectomy "should be done in any patient in whom anastomotic ulcers continue to recur after adequate vagotomy and partial gastrectomy" Their 3 patients who underwent total gastrectomy had moderately good health afterwards

We review here the experience of 12 patients who underwent total gastrectomy for benign peptic ulcer at the Central Middlesex Hospital

Case 1 —A man, aged 42, was admitted on Oct 11, 1951, with nine years' history of typical ulcer dyspepsia, which had become more severe for eight months before admission, with nausea, vomiting, anorexia, and a loss of weight of 21 lb A barium meal showed an apparently malignant ulcer on the lesser curve of the stomach and involving the antrum At gastroscopy, however, the ulcer appeared to be simple At operation on Nov 24, 1951, an extensive ulcer in the middle third of the lesser curve was found, with many enlarged glands The appearances suggested carcinoma, and a total gastrectomy with end-to-end œsophago-duodenostomy (fig 1) was done Histological examination proved the ulcer to be benign

Postoperative progress —The patient's preoperative weight of 8 st 13 lb had decreased to 7 st 8 lb when he was discharged from hospital After this he gained weight despite the fact that, on radiological examination, barium reached the terminal ileum five minutes after it had been swallowed In August, 1952, he weighed 7 st 11 lb He continued to gain weight and by February, 1953, had reached 8 st 2 lb and could eat a good diet His weight remained steady until February, 1956, when it decreased to 7 st 12 lb and a small lesion was noted in his right lung but was thought to b quiescent By January, 1957, his weight had decreased to 6 st 2 l and tubercle bacilli were found in his sputum He is still receiv antituberculous chemotherapy and is responding slowly Treatment is complicated by the development of streptomycin sensitivity H haemoglobin is 82%.

Summary —A man, aged 42, underwent total gastrectomy with œsophago-duodenal anastomosis for what was histologi cally proved to be a benign ulcer His subsequent course was satisfactory, with gain in weight and a fair appetite, until th development of pulmonary tuberculosis four years and four months after the operation

Case 2 —A woman, aged 47, had a severe hæmatemesis from a duodenal ulcer in 1946 A Polya-type partial gastrectomy was do in 1947 because of continuing ulcer pain. Her symptoms soo returned, and an anastomotic ulcer was found radiologically in 194 In March, 1950, laparotomy was done after a further hæmatemesis, when an anastomotic ulcer and a pancreatic adenoma were found No resection was done at this operation, but in October, 1950, the patient was admitted with a view to a further partial gastrectomy for severe ulcer pain, but she developed a volvulus of the cæcum and underwent a right hemicolectomy, and the partial gastrectomy was done later She had to be readmitted after a hæmatemesis in June, 1951, when another anastomotic ulcer was found She was treated medically A melæna in April, 1952, was treated at home, but in September, 1953, admission to hospital was again necessary becaus of severe hæmatemesis A total gastrectomy was done with an œsophageal anastomosis to the side of a Roux loop of jejunum (fig 5) The patient was discharged after a stormy convalescence due to a subphrenic abscess in December, 1953 In May, 1951, she weighed 8 st 13 lb In March, 1954, six months after the total gastrectomy she weighed 8 st but was eating well and her bowels were regular In March, 1956, she weighed 7 st 7 lb but was well, with regular bowel actions and a good appetite She has remained well since with no further loss of weight

Summary —This woman had a total gastrectomy with Roux-en-Y reconstruction for recurrent anastomotic ulceration Four years later she was well but had lost 20 lb in weight in three years Her weight has not changed since Her hæmoglobin is 90%, and she is doing her housework

Case 3 —A man, aged 31, had a Polya-type partial gastrectomy in 1941 for duodenal ulcer of five years' standing Ulcer symptoms returned in 1943, and he had periods of medical treatment in 1943, 1944, and 1949 In September, 1952, a further Polya type gastrectomy was done for anastomotic ulceration Three months later ulcer symptoms returned once more with some loss of weight, and in September, 1953, a total gastrectomy, with an end to side œsophago-jejunostomy and a side-to-side entero-enterostomy between afferent and efferent loops (fig 3), was done for a large anastomotic ulcer The patient made an uneventful recovery In November, 1952, after the second partial gastrectomy, he weighed 10 st 5 lb and in September, 1953, 10 st 3 lb In January, 1954, four months after the total gastrectomy he weighed 9 st 5 lb and had a fair appetite but was troubled by heartburn, bilious vomiting, and dysphagia A barium meal, however, showed a normally functioning anastomosis His symptoms remained unchanged, but he continued to lose weight until March, 1956, when he weighed 8 st 10lb Revision of the anastomosis was considered at this time, but it was thought that the symptoms did not warrant the risks involved When last seen in August, 1957, four years after the total gastrectomy,

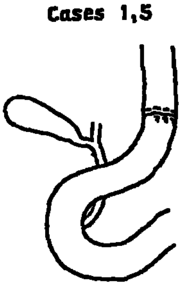

Fig 1—End-to-end œsophago-duodenal anastomosis

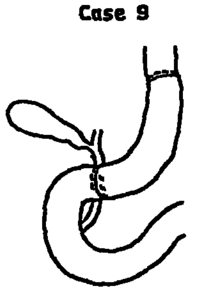

Fig 2—Jejunal-loop replacement with œsophago - jejunal and jejuno-duodenal anastomoses

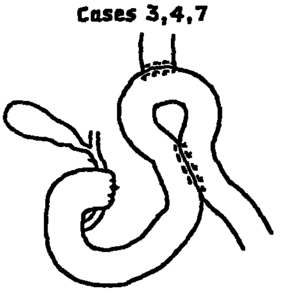

Fig 3—End-to-side œsophago-jejunal anastomosis with side-to-side jejuno-jejunostomy

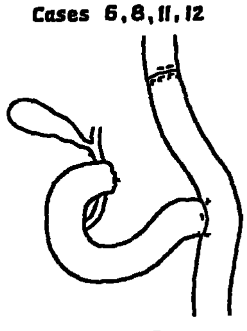

Fig 4—Roux-en-Y reconstruction with end-to-end œsophago-jejunal anastomosis

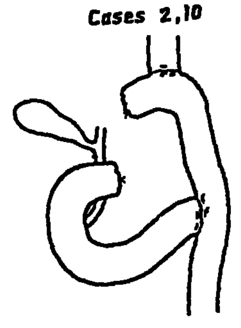

Fig 5—Roux-en-Y reconstruction with end to-side œsophago-jejunal anastomosis

the patient still had heartburn, bilious vomiting, and a poor appetite, but his weight was steady at 8 st 10 lb His hæmoglobin was 89% He is at work

Summary.—This man had recurrent anastomotic ulceration following a Polya-type partial gastrectomy for duodenal ulcer, it recurred after a further gastrectomy Total gastrectomy, with an end-to-side œsophago-jejunal anastomosis and a side-to-side entero-enterostomy between afferent and efferent loops, was done four years ago He has lost 23 lb and is troubled by heartburn, bilious vomiting, and a poor appetite but he is able to work.

Case 4.—A man, aged 52, presented in December, 1953, with eighteen months' history of loss of weight (3 st.), epigastric discomfort, and anorexia A barium meal showed deformity of the pyloric antrum suggesting carcinoma At operation the antrum was found to be indurated and the subpyloric glands enlarged and hard A total gastrectomy, with end-to-side œsophago-jejunostomy and side-to-side entero-enterostomy between afferent and efferent loops (fig 3), was done The patient made an uneventful recovery Histological examination of the resected stomach and glands revealed no evidence of malignancy In October, 1953, two months before the operation, he weighed 12 st. 9 lb By March, 1954, six months later, his weight had decreased to 11 st. 12 lb , his appetite was poor, and he complained of bilious regurgitation and dysphagia A barium meal, however, showed no hold-up By August, 1954, there was some improvement in appetite and energy, but the bilious regurgitation persisted, and he had lost another 3 lb in weight He was last seen in June, 1955, eighteen months after the total gastrectomy, when his condition was unchanged His hæmoglobin was 92% He could not be traced in November, 1956, having moved from London

Summary—This patient had a total gastrectomy, with an end-to-side œsophago-jejunal anastomosis and side-to-side entero-enterostomy between afferent and efferent loops, on the mistaken radiological and operative diagnosis of carcinoma of the pyloric antrum After this he lost 14 lb in weight and has had troublesome bilious vomiting

Case 5—A married woman, aged 71, was admitted in December, 1953, with severe ulcer dyspepsia and melæna She had had previous bouts of ulcer dyspepsia in 1913, 1943, 1951, and 1952 Gastroscopy showed an hour-glass deformity of the stomach and three gastric ulcers A barium meal was reported as showing a single ulcer At operation the appearances were those of a gastric carcinoma, and a total gastrectomy with an end-to-end œsophago-duodenostomy (fig 1) was done The postoperative course was uneventful Histologically the gastric ulcer was benign, but a leiomyoma was also found near by Before the operation the patient weighed 7 st 6 lb , three months later, in March, 1954, she weighed 7 st 3 lb , could eat normal meals, and was feeling well, and her bowels were regular She had palpitations and faintness sometimes, mainly after sweet foods Since then she has improved steadily, with increasing appetite, energy, and weight, and fewer dumping symptoms When last seen in May, 1957, she weighed 7 st 13 lb , could eat anything, and had regular actions of her bowels Her hæmoglobin was 84%

Summary—This old lady had a total gastrectomy with an end-to-end œsophago-duodenostomy because of the operative diagnosis of gastric carcinoma, which was proved to be erroneous She has gained 10 lb in weight since the operation and is in excellent health three and a half years later

Case 6.—A man, aged 47, underwent partial gastrectomy for a duodenal ulcer of ten years' standing Ulcer pain recurred a year later, and he lost a great deal of weight in the next three years In January, 1954, a barium meal showed a large anastomotic ulcer, so a total gastrectomy with a Roux-en-Y œsophago-jejunal reconstruction (fig 4) was done His postoperative course was marred by a wound infection, but he made a good recovery Before the original partial gastrectomy he weighed 10 st., but by October, 1953, his weight had decreased to 9 st 5 lb After the total gastrectomy he lost weight despite a good appetite and regular bowel actions He reached his lowest weight—8 st 12 lb —in July, 1954, but since then he has gained weight and when last seen in April, 1957, he weighed 9 st 3 lb He was then well, with a good appetite and energy, occasional bulky stools, and a mild iron-deficiency anæmia (Hb 80%)

Summary—This man, aged 51, had a total gastrectomy with a Roux-en-Y reconstruction in January, 1954, for anastomotic ulcer Three years later he is well, with a good appetite and energy His weight is almost the same as before total gastrectomy

Case 7—A boy, aged 15, had duodenal-ulcer dyspepsia in 1940 He had a perforation and hæmatemesis in 1942, while in the Merchant Navy, a partial gastrectomy was done in 1948, a further gastrectomy, with a vagotomy, was done in 1950 for anastomatic ulcer He was treated medically in 1952 for another anastomotic ulcer, and in 1953 a gastrocolic fistula was repaired A further vagotomy was attempted in 1954, but later that year a further gastric resection was necessary Within a few months the patient had his sixth anastomotic ulcer, and a total gastrectomy, with end-to-side œsophago-jejunostomy and side-to-side entero-enterostomy between the afferent and efferent loops (fig 3), was done in February, 1955 Convalescence was complicated by an empyema, which resolved with conservative treatment. In 1950, at the time of his third gastrectomy, he weighed 7 st 5 lb After the repair of the gastrocolic fistula his weight fell to 6 st 9 lb At this time he had very severe steatorrhœa, which persisted after the total gastrectomy, his weight two months later being only 6 st Since then, however, his condition has improved slowly, and when last seen in January, 1957, two years after the total gastrectomy, he was regaining some appetite and his weight had increased to 8 st 2 lb He is still troubled by steatorrhœa, but this can be controlled partially by aureomycin

Summary—This young man had his first partial gastrectomy at the age of 23 After further resections and vagotomy had failed to prevent the recurrence of ulcers, the sixth recurrence was treated by total gastrectomy, the œsophagus being anastomosed to the side of a jejunal loop, with entero-enterostomy between afferent and efferent loops Severe steatorrhœa persisted after this operation, but the patient has managed to gain weight.

Case 8.—A man, aged 38, had melæna in 1917 He was operated on in 1924 at another hospital and again in 1929 for further hæmorrhages He had twelve further attacks of melæna up to 1943, when, after yet another severe melæna, a Polya-type partial gastrectomy was done for duodenal ulcer In the next twelve years the patient had sixteen more episodes of gastrointestinal hæmorrhage He had never had ulcer pain He had always bled profusely from cuts, but a full investigation of his blood by Dr J V. Dacie revealed no abnormality By the time he was referred to the Central Middlesex Hospital in March, 1955, he had had 200 bottles of blood by transfusion At this time a total gastrectomy with a Roux-en-Y reconstruction (fig 4) was done for a large anastomotic ulcer He made a good recovery In November, 1956, eighteen months after the total gastrectomy, his general practitioner reported " I think he could eat a larger meal than I " He was gaining weight and at work. In November, 1957, he wrote " I feel very fit and in the best of health My weight is nearly 12 st With regard to food, I can eat anything, usually four good meals a day "

Summary—This patient had recurrent gastrointestinal hæmorrhages between 1917 and 1955 and received 200 pints of blood by transfusion The hæmorrhages continued despite three gastric operations, the last a Polya-type partial gastrectomy A total gastrectomy with a Roux-en-Y reconstruction was done in March, 1955, and in November, 1957, the patient is in excellent health

Case 9.—A man, aged 32, was seen in 1946 with four years' history of ulcer dyspepsia A barium meal confirmed the diagnosis of duodenal ulceration The ulcer perforated in 1950 and was treated by suture In August, 1951, a Polya-type partial gastrectomy was done, but, because of continuing loss of weight, was refashioned to a jejunal-loop replacement gastrectomy in January, 1952 In February, 1953, streptococcal liver abscess developed and required surgical drainage In March, 1954, ulcer pain returned, and an anastomotic ulcer was found in the jejunal segment. This was resected and a Billroth-I anastomosis made While the patient was still in hospital another anastomotic ulcer developed, and a vagotomy was done but failed to cure the ulcer, which persisted despite medical treatment In April, 1955, a total gastrectomy, with a jejunal segment replacement (œsophago-jejuno-duodenal anastomosis) was done (fig 2) Postoperative convalescence was uneventful Before the first partial gastrectomy this patient weighed 9 st 6 lb , and just before the total gastrectomy, despite his stormy career, 9 st 2 lb Six months later his weight was 8 st 8 lb and it has remained unchanged since When last seen in August, 1957, he was still complaining of epigastric fullness after meals and some pain and nausea He has mild steatorrhœa, but his hæmoglobin is 92%

Summary—This man had an unsuccessful Polya partial gastrectomy in August, 1951 Conversion to a jejunal-loop replacement gastrectomy was followed by recurrent anastomotic ulceration, which was not cured by conversion to a Billroth-I

SUMMARY OF DATA OF 12 PATIENTS TREATED BY TOTAL GASTRECTOMY FOR BENIGN PEPTIC ULCER

Case no	Sex	Age at T G (yr)	Reason for T G	Type of reconstruction	Weight before T G (lb)	Weight at F U (lb)	Length of F U (ms)	Results
2	F	54	A U	Roux-en-Y	125	105	50	Good
6	M	51	A U	Roux-en-Y	129	128	39	Very good
8	M	56	A U	Roux-en-Y	Not known	Increasing	32	Very good
10	F	34	A U	Roux-en-Y	87	98	31	Fair (pain in thoracotomy scar)
11	M	54	A U	Roux-en-Y	Not known	Not known	21	Very good
12	M	49	A U	Roux-en-Y	150	149	20	Very good
1	M	48	G U	Œsophago-duodenal anastomosis	125	87	74	Poor (pulm tuberculosis)
5	F	71	G U	Œsophago-duodenal anastomosis	104	111	41	Very good
3	M	45	A U	Loop reconstruction with lateral entero-anastomosis	143	122	48	Poor
4	M	52	G U	Loop reconstruction with lateral entero-anastomosis	177	162	18	Fair
7	M	31	A U	Loop reconstruction with lateral entero-anastomosis	93	114	24	Fair (steatorrhœa)
9	M	47	A U	Jejunal replacement œsophago-jejuno-duodenal anastomosis	128	120	28	Fair

A U, anastomotic ulcer F U, follow-up G U, gastric ulcer T G, total gastrectomy

reconstruction or by vagotomy In April, 1955, total gastrectomy with a jejunal-loop replacement was done The result has been only moderately good

Case 10 —A married woman, aged 23, began to have ulcer symptoms in 1944 and shortly afterwards a duodenal ulcer perforated and was sutured By May, 1950, pyloric stenosis had developed, and a gastroenterostomy was done Eighteen months later ulcer symptoms recurred, and an anastomotic ulcer was found in August, 1953, and was treated by a Polya-type partial gastrectomy Ulcer pain recurred again within three months, but no anastomotic ulcer was found The patient was referred to the Central Middlesex Hospital in April, 1955, and a barium meal now showed an anastomotic ulcer Total gastrectomy with a Roux-en-Y reconstruction (fig 5) was done Postoperative convalescence was uneventful We have no record of her earlier weight, but two months after the total gastrectomy she weighed 6 st 4 lb She then complained of retrosternal discomfort after meals but was otherwise well In January, 1956, nine months after her operation, she was readmitted with retrosternal pain radiating to her shoulders Physical examination, barium meal, and œsophagoscopy were unrevealing In December, 1956, she weighed 6 st 8 lb, still had some pain, and had iron-deficiency anæmia (Hb 72%) In November, 1957, her general practitioner reported that she now weighed 7 st, her appetite was fair, and her hæmoglobin was 90% He wrote "Having had so much trouble in the past, she finds it difficult to believe she has not another ulcer " She is doing her housework

Summary —This young woman had an unsuccessful gastroenterostomy for a duodenal ulcer with pyloric stenosis in 1950 A Polya-type partial gastrectomy was done in 1953 for anastomotic ulceration This recurred, and in April, 1955, total gastrectomy with a Roux-en-Y gastrectomy was done She still complains of chest pain but has gained weight and has a fair appetite

Case 11 —A man, aged 30, began to have ulcer dyspepsia in 1931 In 1933 he had a gastroenterostomy for duodenal ulcer The ulcer pain returned twelve years later, and in 1945 a further operation was done In 1947 and in 1949 further anastomotic ulcers were excised, and in 1951 a vagotomy was done for yet another ulcer In 1953 a further ulcer caused a hæmatemesis, which was treated medically, and in April, 1955, a large anastomotic ulcer, adherent to the eighth rib anteriorly, was excised In November, 1955, the patient was referred to the Central Middlesex Hospital, where a barium meal showed a large stomal ulcer He was readmitted in January, 1956, and total gastrectomy with a Roux-en-Y reconstruction (fig 4) was done His postoperative course was uneventful In November, 1957, twenty-two months after the total gastrectomy, his general practitioner reported that the patient had given up using pethidine, had an excellent appetite, and was gaining weight The doctor wrote "He is absolutely marvellous compared to the old days I am most impressed with this case as the transformation is astonishing "

Summary —This man had a series of anastomotic ulcers excised and vagotomy done after an initial gastroenterostomy for duodenal ulcer Total gastrectomy in January, 1955, with Roux-en-Y reconstruction has given a very good result, judged twenty months later

Case 12.—A man, aged 27, began to have ulcer dyspepsia in 1934 A perforation of a duodenal ulcer followed in 1939 In 1943 a Polya-type partial gastrectomy was done In 1944, 1947, and 1951 he had perforations of anastomotic ulcers treated by suture He continued to have ulcer pain for the next two years and had melæna in 1952 After this he was well for two years, but in September, 1955, he was admitted with a perforated anastomotic ulcer and had a subtotal Polya-type gastrectomy In December, 1955, he had another anastomotic ulcer He was admitted in February, 1956, and underwent total gastrectomy with a Roux-en-Y reconstruction (fig 4) His postoperative convalescence was uneventful In April, 1955, during a period of relatively good health, he weighed 10 st 10 lb In April, 1956, two months after the total gastrectomy, he complained of heartburn at night but was able to eat a full meal He was troubled by constipation, for which he took 'Senokot' His weight was 10 st 1 lb By June, 1956, he was back at work, and when last seen in November, 1957, twenty months after his total gastrectomy, he was very well, could eat anything, and weighed 10 st 9 lb He said "Why did you not do this operation ten years ago?"

Summary —This man had a series of anastomotic ulcers following a Polya-type partial gastrectomy in 1943 In September, 1955, a subtotal gastrectomy was done for yet another perforated anastomotic ulcer, but two months later anastomotic ulceration had recurred, and in February, 1956, total gastrectomy with a Roux-en-Y reconstruction was done, with very good results

Conclusions

No total gastrectomy for benign ulcer was done at the Central Middlesex Hospital before 1951 Since then 12 patients have had this operation for benign ulcer, and all have survived In 9 patients the operation was done for recurrent anastomotic ulceration, in the remaining 3 patients the lesion was a gastric ulcer, mistaken for carcinoma at operation

The accompanying table summarises the results obtained in these 12 patients There is no doubt that those patients who had the Roux-en-Y reconstruction have had the best results Of these 6 patients (cases 2, 6, 8, and 10–12), all operated on for anastomotic ulcer, 4 are very well, eating normal meals, and leading normal lives twenty to thirty-nine months after the operation 1 other patient is well but has lost 20 lb in weight, but other factors may be partly responsible, and the remaining 1 is well in every way but continues to be troubled by pain in the thoracotomy scar 3 patients (cases 3, 4, and 7) have had loop reconstructions with lateral entero-anastomosis, none of these has been really successful, though they are able to work 1 has severe steatorrhœa, present even before total gastrectomy, but has managed to gain weight with the aid of aureomycin The 2 others have lost weight and are troubled by bilious vomiting and heartburn Direct œsophago-duodenal anastomoses were done for 2 patients (cases 1 and 5), with excellent results in 1 The other patient has no dyspeptic symptoms but has contracted severe pulmonary tuberculosis four years and four months after the operation

The creation of an artificial gastric reservoir from a jejunal loop has not been a success in the 1 case where this was done (case 9) These results agree with the experience with patients undergoing total gastrectomy for carcinoma at the Central Middlesex Hospital Brintnall et al (1956), on the basis of a careful analysis of 58 patients with total gastrectomy mainly for carcinoma, also concluded that the Roux-en-Y reconstruction (24 patients) gave the best results They too were disappointed with the results of direct œsophago-duodenal anastomosis (3 cases), mainly because of loss of weight and bilious regurgitation They found that iron was the only factor required in larger than normal amounts in their patients

All our patients have had regular doses of intramuscular vitamin B_{12}, and no instance of macrocytic anæmia has been found among them Iron-deficiency anæmia, however, is liable to occur, and we agree with Brintnall et al (1956) that these patients need additional oral iron, in the same way as do patients who have undergone partial gastrectomy

From our experience with these 12 patients we feel that total gastrectomy, if done with a Roux-en-Y reconstruction, is a justifiable operation for patients with anastomotic ulceration not cured by an adequate partial gastrectomy and vagotomy, and even in patients with simple gastric ulcer in whom, at operation, the findings strongly suggest malignancy and in whom subtotal resection would not have given sufficient clearance Adequate maintenance doses of vitamin B_{12} and oral iron are essential for the well-being of these patients In our experience the nutrition of patients with Roux-en-Y reconstructions is entirely satisfactory They can eat a normal amount of food and can maintain their weight

Summary

The case histories of 12 patients who have had total gastrectomy for benign peptic ulcer are presented

The Roux-en-Y reconstruction gives satisfactory results and is to be preferred to other methods of reconstruction The operation is justified in patients with obstinate anastomotic ulceration not arrested by adequate gastrectomy and vagotomy

The nutrition of patients with the Roux-en-Y reconstruction is satisfactory They must, however, be given regular maintenance doses of vitamin B_{12} and oral iron

These patients were all admitted to the Gastroenterological Unit of the Central Middlesex Hospital under the care of Dr F Avery Jones, to whom we are indebted We also wish to thank our colleagues, Mr T G I James, Mr F A Henley, and Mr H Hasheman

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URICOSURIC EFFECT OF DICOUMAROL

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SINCE dicoumarol was introduced about fifteen years ago into therapy by Butt et al (1941) and Lehmann (1942) it has been increasingly used prophylactically and therapeutically in conditions connected with thrombo-embolism The attention of pharmacologists and clinicians has been focused on its effect on clotting of the blood by hampering the formation of proconvertin and prothrombin in the liver Some workers look on this as its sole pharmacological action (Møller 1955, Goodman and Gilman 1955), but this standpoint is no longer tenable

TABLE I—SERUM URIC-ACID LEVELS (MG PER 100 ML) IN SERUM BEFORE AND AFTER DICOUMAROL IN HEALTHY PERSONS

—	Person no				
	1	2	3	4	5
Before	5 3	4 9	5 4	4 1	6 1
After	3 7	4·4	4 4	3 4	5 0
% fall	30	10	19	17	18

Sougin-Mibashan and Horwitz (1955) investigated the effect of 'Tromexan' (ethylbiscoumacetate) on the metabolism of uric acid in the rat, the dalmatian dog, and man, using Brown's colorimetric method for determining the uric acid (Kolmer and Boerner 1945) After a single dose of tromexan 1 2–1 8 g by mouth they found a pronounced fall in the level of uric acid in the serum and a significant rise in the ratio of uric-acid clearance to creatinine clearance

We have investigated whether dicoumarol produces similar effects We estimated the uric acid in both serum and urine by enzymatic spectrophotometry by the method of Prætorius (1949) modified by Prætorius and Poulsen (1953) All the determinations were made as double determinations, the deviations from the average rarely exceeding ±3%

Material and Method

The levels of uric acid in the serum were determined in 40 patients before and during anticoagulant treatment 27 patients had myocardial infarction, in 9 patients this disease was suspected, 3 had pulmonary embolism, and 1 had undergone a bypass operation on a femoral artery

The anticoagulant treatment was given according to principles described by Holten (1955) Initially a dose of 500–750 mg of dicoumarol was given, after which dicoumarol was withheld for two or three days The next dose depended on the effect of the initial dose on the prothrombin time, and the daily maintenance dosage was adapted according to daily determinations of the prothrombin time During the first two days after the start of treatment intramuscular long-acting heparin 15,000–20,000 I U was injected at intervals of eight hours

To determine the effect of dicoumarol on the uric-acid level in the serum under comparable conditions we chose as standard the first fasting sample taken and related this to the lowest level of uric acid in the serum after the initial dose of dicoumarol

Results

In the vast majority of cases the level falls During treatment with the maintenance dosage of dicoumarol the uric-acid level in the serum rises again to a fairly constant value, which in almost all cases is lower than that of the first fasting sample

The average fall was 1 8±0 2 mg per 100 ml In 31 patients—i e, more than 75%—the level of uric acid in the serum fell more than 20%, in 4 patients it fell 10–20%, and in 5 patients no significant change was observed The possibility that this fall might be due to the myocardial infarction or to the heparin was investigated by determining the level of uric acid in the serum before and after a dose of 500–700 mg of dicoumarol in 5 healthy persons (table I)

The uric-acid levels in the serum were determined at least thrice during the first twenty-four hours after the administration of dicoumarol and subsequently daily for three to seven days In table I the lowest levels after dicoumarol are given, these were usually found twenty-four hours after the administration of dicoumarol

TABLE II—SERUM LEVELS, EXCRETION, AND CLEARANCE OF URIC ACID AND CLEARANCE OF CREATININE

Person no	Day no	Uric acid in serum (mg per 100 ml)	Urinary excretion of uric acid (mg per 24 hr)	Clearance (ml. per min.)	
				Uric acid	Creatinine
4	1	4 1	714	11 4	161
	2	4 0	777	11 7	107
	3	4 1	944	15 2	132*
	4	3 8	860	15 4	126
	5	3·4	691		118
	% difference	−17	+27	+31	
5	1	6 1			100
	2	5 7	426	4 9	70
	3	5 2	482	5 8	70
	4	4 9	445	4 6	65
	5	5 7	625	7 4	67*
	6	5 0	621	7 0	104
	7	5 2	517		
	% difference	−18	+39	+45	

* Dicoumarol 500 mg was given after fasting blood-samples had been *drawn at the beginning of days 3 and 5*

In 2 of the healthy persons (nos 4 and 5) the urinary excretion of uric acid in twenty-four hours was determined for several days, simultaneously the clearance of endogenous creatinine was determined The results are given in table II

Discussion

These results show that dicoumarol increases the urinary excretion of uric acid and decreases the level of uric acid in the serum It is generally believed that uric acid is freely filtered in the glomeruli, and that about 90% of the uric acid filtered is reabsorbed in the tubules Since the clearance of creatinine is not changed while that of uric acid increases after the administration of dicoumarol, dicoumarol probably decreases the tubular reabsorption of uric acid

The well-known uricosuric drugs have similar actions This has been shown for probenecid by Gutman and Yu (1951), for salicylic acid by Crone and Lassen (1955) and for tromexan by Sougin-Mibashan and Horwitz (1955)

This uricosuric effect of the coumarin derivatives is of interest in connection with the significance of the level of uric acid in the serum in the pathogenesis of atherosclerosis Huchard (1899) compared the changes in the arteries in uric arthritis with the changes in the heart in rheumatic fever, and Roberts (1900) mentioned the significance of "uric-acid diathesis" for the development of thromboembolic processes Gertler and White (1954) mention the possible significance of uric acid in the serum as a harmful agent causing deposition of cholesterol The question arises do the coumarin derivatives improve the prognosis of myocardial infarction solely by their anticoagulant effect, or is their uricosuric effect also important? At any rate it is well established that the effect on clotting is not the only effect of the coumarin derivatives

Summary

In 40 patients with myocardial infarction and other thromboembolic conditions dicoumarol in initial doses of 500–750 mg caused an average decrease of 1 8±0 2 mg per 100 ml in the level of uric acid in the serum On maintenance doses of dicoumarol this level rose a little but not to its pre-treatment value

In experiments on healthy volunteers dicoumarol caused a significant fall in the level of uric acid in the serum and increased urinary excretion of uric acid, probably because dicoumarol hampers tubular reabsorption

References at foot of next column

FRACTURES OF THE PARIETAL BONE IN CHILDREN

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There is a type of fracture of the parietal bone in children with distinctive clinical features In 1955-57 twelve such cases were seen in the casualty department of the General Infirmary at Leeds, in which 38,000 new cases annually are treated

Clinical Picture

An anxious parent brings to the casualty department a small child with a lump on the side of its head and a history of a fall on to its head some days previously After the initial upset the child went on eating, sleeping, and playing as before The parent found nothing wrong with the head shortly after the fall but discovered some days later (in this series 1–14 days) a lump on the side of the head In the casualty department the child is found to be perfectly healthy with no physical signs except the lump

The lump has special characteristics In some children rather long hair over it makes it difficult to see without careful scrutiny Palpation, however, reveals a soft cystic swelling on one side of the head and of appreciable size—usually 3 or 4 inches in diameter It is roughly circular and not bounded by any of the suture lines of the skull Its edge is fairly easy to define but not clearcut There is no bruising in the overlying skin or superficial fascia The swelling is uniformly soft and bears no resemblance to the ordinary hæmatoma of the scalp, with its soft centre and firm edge

Diagnosis

A fracture of the underlying parietal bone can be confidently diagnosed on the physical characteristics of the swelling alone In ten of these cases immediate radiography revealed a linear fracture of the parietal bone, sometimes running into the neighbouring bones The size of the fracture bore no relation to the size of the swelling In one case, however, radiography two days after the injury, and again three days after, showed no fracture, but fourteen days later revealed the fracture line very clearly These eleven patients were aged from 6 months to 3 years The twelfth case was in a boy, aged 9 years, in whom radiography at his first attendance and twice subsequently, revealed no fracture, but nevertheless the clinical features and characteristics of the swelling were typical

Course

The courses of these cases were very similar The child remained perfectly well The swelling remained

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unchanged in size for some days and then relatively abruptly began to disappear it shrank in size, diameter, and depth, but its consistence remained unchanged In a few days the swelling completely disappeared, leaving no trace In the eleven cases in which a fracture was demonstrated radiographically the swelling disappeared 12–21 days after it had appeared In the boy aged 9 years the swelling took 32 days to disappear In eleven of these twelve patients there were no further symptoms The twelfth patient, a boy aged 18 months, returned four months later with a history of four days' swelling in the same site, of apparently spontaneous origin Radiography showed the fracture line to be still present The subsequent course of this swelling was the same as that of the other swellings it disappeared in three weeks and has not recurred

Discussion

A search of standard surgical textbooks and special textbooks on head injuries revealed no reference to this swelling in association with a fractured parietal bone A search of the medical literature was equally without result Several articles have been published by radiologists describing fractures of the skull in children Ireland (1932) states that fracture of the parietal bone is the commonest fracture of the skull in children He points out that the fracture line in the parietal bone often runs into the neighbouring bones (as in many of the present cases) He makes no reference to any associated swelling overlying the fracture Pia (1953), who reviewed the literature on fractures of the skull in children and described a large number of personal cases, made no reference to the associated swelling in fractures of the parietal bone

The nature and site of this swelling are of considerable interest Because the swelling shows no overlying bruising and is not delimited by the suture lines of the skull, it is postulated that the swelling lies between the galea aponeurotica and the periosteum of the skull Investigation of the nature of the fluid, however, is hindered by consideration for the patient When experience has shown that the swelling is absorbed spontaneously, it is unjustifiable to subject a small child to elaborate investigations In the baby girl, aged 15 months, whose swelling and radiograph are shown in figs 1 and 2, the swelling was so large that aspiration was considered justified

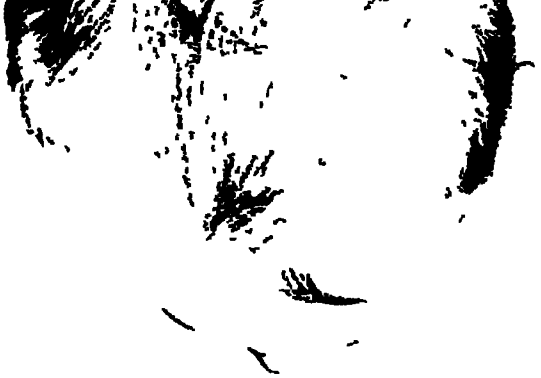

Fig 1—Swelling over parietal bone in baby aged 15 months

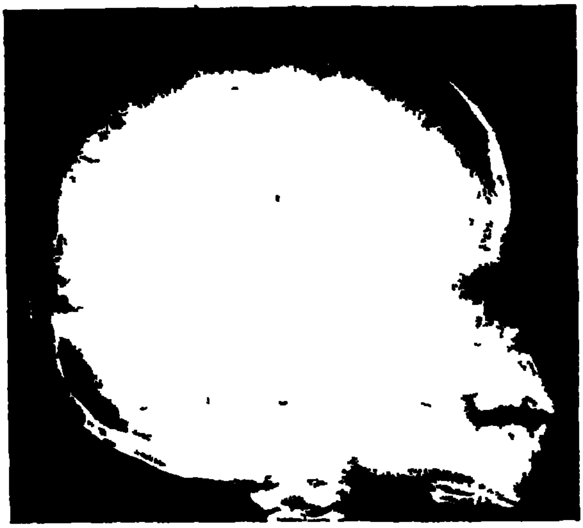

Fig 2—Radiograph of same case as in fig 1

Aspiration through the shaved scalp produced 50 ml of fluid which was heavily contaminated with blood and resembled that obtained by lumbar puncture after subarachnoid hæmorrhage On standing the blood settled in the container, leaving a red-stained thin fluid above it, which was taken to be cerebrospinal fluid (C S F) with some hæmolysis The sugar content of this fluid was consistent with its being C S F

Three days after aspiration a swelling had reappeared about half the original size but of exactly similar consistence Re-aspiration was not considered justifiable This new swelling was completely absorbed in two weeks

It is postulated that with the fracture of the parietal bone there was a subjacent tear of the meninges Leaking C S F mixed with blood oozed through the fracture into the loose tissue spaces below the galea In case 12, in which there was no fracture, fluid is assumed to have oozed between the suture lines Lumbar puncture would probably yield bloodstained fluid and support this theory It will be appreciated, however, that there was great reluctance to submit these children to such an unpleasant investigation, which was really only of academic interest

It seems fairly clear that, in these cases, there is no danger of intracranial compression, and all these patients were treated as outpatients

Summary

Twelve small children in whom a soft swelling developed over a parietal bone some days after an injury are reported In eleven cases there was a subjacent fracture of the parietal bone, and the swelling was spontaneously absorbed within three weeks

This type of swelling associated with fracture is apparently hitherto undescribed

It is postulated that this swelling is due to a leak of C S F and blood from a subjacent tear of the meninges, through the fracture line into the space below the galea aponeurotica

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Preliminary Communication

THE MEMBRANE OXYGENATOR

SOME ASPECTS OF OXYGEN AND CARBON DIOXIDE TRANSPORT ACROSS POLYETHYLENE FILM *

CARDIAC surgery has entered a new phase in its development Operations within the chambers of the heart are commonplace, and most are possible because machines take the place of cardiopulmonary function during such surgery In the design of these machines the most vexed question remains the choice of method for gas exchange There is a general leaning towards the principle of imitation of the normal pulmonary anatomy, where the blood is separated from the gas by a membrane Pursuit of this ideal is exemplified by the continuing work of Clowes [1] and Kolff [2]

During experiments with a design made by one of us (M L B) of an oxygenator provided with a membrane certain factors have emerged which may alter the direction of emphasis in the search for the ideal membrane, and we have felt it of sufficient interest to report some of these initial experiments They underline the importance of the character of such membranes in regard to the transport of carbon dioxide and indicate that this property may be of greater significance than has hitherto been realised

METHOD

The membrane chosen for these studies was polyethylene $^1/_{1000}$ inch thick It was supplied by the Visking Corporation, of Centerville, California The mechanical description of the lung will be published elsewhere

The design tested provided a surface area of 9 5 sq m for gas exchange and allowed a blood-flow of 3 litres a minute Ancillary reservoirs, tubing, and a roller pump of DeBakey type, together with the oxygenator, contained 3 litres of blood and hence allowed a recirculation time of one minute for the blood contained

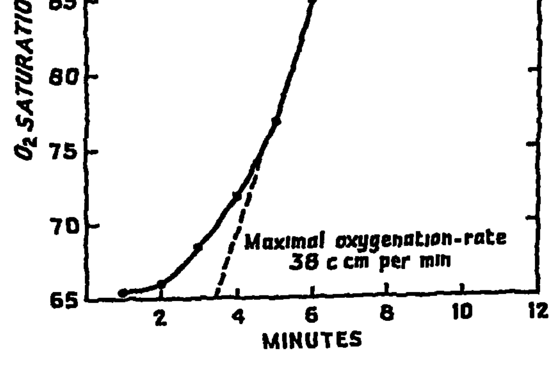

Fig 1—Change in oxygen saturation of blood on admission of oxygen into membrane lung

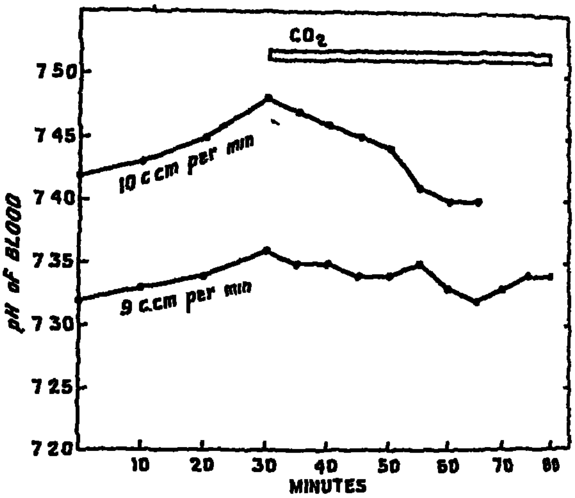

Fig 2—Change in pH before and after carbon dioxide is added to blood at 9 c cm a minute and at 10 c cm a minute

The flow of gas through the apparatus was more than 60 litres a minute to avoid stagnation The respiring gas was recirculated through a carbon-dioxide absorber and through a gas heater, which could maintain a constant temperature after the apparatus had been preheated to the required degree

For all the experiments beef blood was drawn from the slaughterhouse on the day of the study It was introduced after the apparatus had been thoroughly rinsed with warm saline solution and after the gas spaces had been completely filled with nitrous oxide This latter precaution allowed recirculation of blood within the apparatus without appreciable alteration in the oxygen saturation and thus ensured proper filling and mixing After repeated measurements for oxygen content had established a steady state, the nitrous oxide was vented, and its place was taken by oxygen admitted at a rate of more than 30 litres a minute Thereafter samples were withdrawn at one minute intervals until again a steady state was reached The measurements of oxygen content were made by cuvette oximeter †

During this period the blood pH was measured at five-minute intervals ‡ Such measurements were continued throughout the study

After the rate of oxygen transport across the membrane had been determined, the ability to excrete carbon dioxide was estimated This gas was added directly to the blood as it entered the oxygenator Injections were made at a rate which was either at or in excess of the expected rate of excretion calculated from the permeability coefficient and the partial pressure of carbon dioxide [3]

To eliminate inefficient absorption of carbon dioxide in the ventilating system a sample of the circulating gas was drawn continuously through a Liston-Becker CO_2 analyser,§ and at no time during the study was the presence of measurable amounts of carbon dioxide detected

RESULTS

The results indicate that the average diffusion-rate of oxygen into the blood was 38 c cm a minute in the described circumstances (fig 1)

Only an average of 9 c cm of carbon dioxide a minute could be added to the blood in these circumstances without causing a considerable change in the pH An increase to 10 c cm a minute depressed the pH uniformly (fig 2)

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* Aided in part by U S Public Health Service Grant no H2192C2

[1] Clowes, G H A in Extracorporeal Circulation (edited by J Garrott Allen), p 81 Springfield, Ill and Oxford 1958

[2] Kolff, W J Effler, D B Groves, L K, Peereboom, G, Moraca, P P Cleveland Clin Quart 1956, 23, 69

† Waters Conley Co, Rochester Minnesota Cuvette XC-50B no 297

‡ Cambridge Instrument Co Ossining New York Model R

§ Liston Becker Plant Beckman Instrument Co Springdale Connecticut

[3] Kammermeyer K Industr Engng Chem 1957 49 1695

n the absence of appreciable metabolism of the blood uring the test it was inferred that the depression of the H represented a failure of the membrane to excrete the dded carbon dioxide at the rate of its addition

DISCUSSION

Plastic membranes have clearly defined characteristics in respect to the passage of gases across them, and it has become established practice to use such membranes for the continuous separation of gaseous mixtures by fractional diffusion Those in use in blood oxygenators at present are no exception to these laws

The ratio of permeability values for oxygen and carbon dioxide when polyethylene is the membrane is

$$\frac{\text{Permeability coefficient of } CO_2}{\text{Permeability coefficient of } O_2}=4$$

Hence four times as much carbon dioxide as oxygen may be expected to pass through a given membrane at the same partial pressure To achieve worthwhile efficiency in present oxygenator designs it is usual to maintain an environment of 100% oxygen outside the membrane and thus a partial pressure of about 750 mm Hg, but to maintain an acceptable blood pH the partial pressure of carbon dioxide in the blood cannot rise much above 50 mm Hg In fact, a partial pressure ratio of 15 to 1 could exist in favour of oxygen diffusion

In these circumstances the relatively greater diffusion-rate (four times) of carbon dioxide is insufficient to counteract the partial pressure ratio, and therefore carbon dioxide can only be transported at about a quarter of the rate obtaining for oxygen Similar characteristics must apply to all membranes whose function depends solely on gaseous diffusion, and, only if the permeability ratio for CO_2/O_2 were about 15, could a respiratory quotient of 1 be maintained in the presence of pure oxygen

The results obtained in the present study (that 38 c cm of oxygen but only 9 c cm of carbon dioxide could be exchanged across the polyethylene membrane) support these theoretical considerations and closely parallel the expected values We are thus forced to accept certain principles in the design of a membrane oxygenator Where *gaseous diffusion is the only mechanism of gas exchange* the rate of diffusion of carbon dioxide is the "bottleneck" determining the area of membrane required In the case of the polyethylene film studied this requirement necessitates a surface area four times as large as would be required for oxygenation with pure oxygen, which would involve the construction of an apparatus providing more than 250 sq m of surface area if adult man is to be adequately respired—for practical reasons an impossibility

Fortunately, much more efficient alternatives to polyethylene exist, but it seems unlikely from the known characteristics of such membranes that they will allow of a carbon-dioxide/oxygen diffusion ratio greater than 5 to 1 This infers that, if oxygenation demands cannot adequately be met when room air is the respiring gas, some other type of membrane will have to be found

Hitherto the search for effective membranes has been confined to those whose surface is "non-wetting" Such surfaces are inherently kind to blood and are desirable from this standpoint, but they do not allow use being made of an important physical property of carbon dioxide This is its solubility in water 25 times as great as that of oxygen It is this property which is used in the animal lung, and it may reasonably be inferred that the principal mechanism of transfer of carbon dioxide across a water-absorbent membrane is its passage as dissolved carbon dioxide

It may therefore be desirable to include the characteristics of "wetting" in the specifications of an ideal membrane Perhaps it may even be advantageous to use two types of membrane in such an oxygenator to obtain the greatest efficiency for both oxygen and carbon-dioxide transport

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Medical Societies

ASSOCIATION OF CLINICAL PATHOLOGISTS

THE Association's 60th general meeting was held at Trinity College, Dublin, on April 18 and 19 We publish below brief accounts of some of the papers presented at the meeting

Myasthenia Gravis

Dr A. L WOOLF and his colleagues had reported [1] for the first time striking changes in the intramuscular nerve-endings in a case of myasthenia gravis, and similar changes had now been found in two out of a further three cases The changes consisted of sprouting of the distal extremity of the subterminal nerve-fibres (which were sometimes irregularly swollen) and formation of multiple, bizarre, or unduly complex endplates Cholinesterase preparations showed minute deposits of cholinesterase over a wide zone around the endplates, indicating that there were far more sprouts than were detectable with the light microscope alone The changes resembled those seen in myositis, dystrophia myotonica, and thyrotoxic myopathy These diseases had little in common as regards contractility of muscle but all showed evidence of endocrine imbalance Dr Woolf thought the changes in the nerve-endings were the result of muscle-fibre degeneration and lymphorrhages caused by this imbalance, which was also responsible for the disordered contractility

Thyroid Gland after Treatment of Thyrotoxicosis

Dr. R C CURRAN, Dr H ECKERT, and Prof G M WILSON reported that, by searching a hospital's pathological records over many years, 7 cases were found in which the portion of thyroid gland left after partial thyroidectomy was available for histological examination the interval between the surgical operation and the necropsy or biopsy ranged from 1 to 14½ years For comparison, 13 glands treated by therapeutic doses of radioactive iodine had been obtained these 13 patients died in hospital at intervals of a few days to 5½ years after treatment Full necropsies were performed. After partial thyroidectomy, the portion of gland left showed progressively decreasing cellular hyperplasia and increasing colloid storage In the first weeks after treatment with ^{131}I, the irradiated glands showed disruption of follicles, necrosis and damage to epithelial cells, œdema and early fibrosis of the stroma, and widespread vascular lesions, including thrombosis The more chronic effects of radiation treatment included stromal fibrosis and increasing numbers of altered epithelial cells, but more striking were the microfollicular structure and the comparative lack of colloid

The two series of glands also seemed to differ metabolically, as judged by the results of giving a tracer dose of ^{131}I to patients rendered euthyroid by one or other method of treatment In the post-thyroidectomy cases, the level of protein-bound radio-iodine 48 hours after the test dose was almost invariably normal—that is, less than 0 4%—which suggested a normal iodine pool in the thyroid gland In contrast, in the irradiated series, the protein-bound radioiodine remained high on average, suggesting a reduced iodine pool in the thyroid gland, a result apparently in harmony with the histological finding of colloid lack

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[1] Woolf A L Bagnal H J, Bauwens, P, Bickerstaff, E R *J Path Bact* 1956, 71, 173

Histology of Chronic Bronchitis

Dr W K Taylor described the microscopical appearances of biopsy material taken from the carina in 54 cases of chronic bronchitis All cases showed an increase of goblet cells up to 100% of the epithelial cells Transitional-cell metaplasia was a very common finding (60%) and about 12% showed squamous metaplasia Carcinoma-in-situ was seen in a few cases In more than half the sections there was some degree of thickening of the basement membrane In the lamina propria there was often some œdema and, occasionally, dilated lymphatics Plasma cells were not infrequent but polymorphs were rare and no eosinophils were seen Elastic fibres were reduced in number and often absent Fibrosis was uncommon and when present it was fine and diffuse

Bronchiolitis from Nitrous Fumes

Dr A J N Warrack said that nitrous fumes were common in industry (dipping of metals, manufacture of toluene and cellulose, descaling and pickling of steel sheets after firing and rolling) Symptoms varied with concentration of the gas and duration of exposure low concentrations merely provoked mild irritation of the eyes and upper respiratory tract, strong concentrations could cause severe pulmonary œdema Sometimes, however, there was a latent interval of many hours or even days, and symptoms then took the form of dyspnœa, cyanosis, and paroxysmal cough Secondary infection was a danger A man carrying nitric acid in a rubber bucket noticed a leak and held the bucket over another of galvanised iron He was enveloped in thick brown fumes for 30 seconds He felt all right and finished his work Seven days after exposure he sought medical attention, and he was admitted semicomatose and cyanosed to hospital two weeks after the original incident He later died Postmortem examination showed both bronchial trees filled with thick mucopus The lungs were solid and section showed tiny yellow areas with the appearance of purulent bronchiolitis Microscopical examination showed varying degrees of obliterative bronchiolitis from simple epithelial desquamation to complete bronchiolar destruction with surrounding alveolar organisation There was presumably secondary infection of these areas, and it was thus important that antibiotic therapy should be given

Phenol Reaction for Blood-sugar Estimation

Dr T M Healy, reporting on the use of this test for the past two years, said that simple sugars when treated with phenol and concentrated sulphuric acid gave an orange yellow colour, stable for some hours The method gave accurate and consistent results Compared with Folin and Wu's method the results were of comparable accuracy but the phenol method took a third of the time and needed less apparatus and cheaper reagents There had been no accidents with the concentrated sulphuric acid The method was suitable for routine use

Megaloblastic Anæmia of Pregnancy and the Puerperium

Dr C Giles and Dr Eileen M Shuttleworth investigated pregnancy anæmia in 369 patients in Stoke-on-Trent during the twelve months ending Feb 28, 1958 In 67 cases sternal puncture revealed a megaloblastic marrow All patients responded to folic acid Reticulocyte-counts varied from 8% to 33%, and the serum-iron fell after two or three days' treatment 18 out of 53 cases tested had achlorhydria and the fæcal fat was raised in 7 out of 15 patients No seasonal incidence was noted The overall diet during pregnancy was poor in a much higher proportion of megaloblastic anæmias than with other types of anæmia this was particularly evident in the case of meat

Virology and the Clinical Bacteriologist

Dr P N Meenan said that tissue-culture methods of viru isolation had now become so widely used that new agents were constantly being recovered, many of them from apparentl healthy people The clinical bacteriologist had been slow to adopt the newer techniques, perhaps because of an exaggerated idea of their difficulties Using these methods at least 5 viruses of man could be studied, and the value of a hospital laboratory would be enormously enhanced if it adopted such methods The basic equipment was simple a supply of sui able glassware and a deep-freeze cabinet (a secondhand ice cream freezer) for the storage of specimens High-speed centri fuges or even roller-drums were not at first essential Tissue culture media were now standardised and easy to prepare o obtain, simple antibiotic mixtures would eliminate bacterial o fungal contamination For small laboratories the most suitabl tissues were probably trypsinised human amnion or HeL cells, in some laboratories uterus, minced and used as plasma clot cultures, would be more convenient but was not a sensitive

Precocious Puberty due to Chorionepithelioma of th Pineal

Dr J H Stephens, Dr D F Cappell, and Dr J L Emer reported two cases of pineal tumour associated with precociou development in boys

(1) A precociously developed boy of 4 years was admitted wit headache, vomiting, and a tumour of the pineal region This wa treated by X rays, and about 4 weeks later he died suddenly of intra ventricular hæmorrhage At necropsy the cerebral tumour was wholl necrotic but the lungs contained multiple hæmorrhagic nodules wit the structure of chorionepithelioma, from which it was inferred tha the pineal growth was of this nature

(2) *A boy of 10 had signs of somatic and sexual precocity* and mil polyuria About 9 months later nervous symptoms developed, wit diplopia, mild fits, athetoid movements, and drowsiness Examina tion revealed a pineal tumour with hydrocephalus for which a short circuit operation was performed Death followed suddenly from intraventricular hæmorrhage, and necropsy revealed a large hæmor rhagic growth replacing the pineal and invading the adjacent brain substance There were no secondary growths

Despite the known activity of such growths in secreting chorionic gonadotrophin, the development of somatic and sexual precocity was not likely to be attributable to these effects, but it was thought to be similar to that responsible for precocity in other pineal growths—e g, teratomata, and in certain lesions, both tumours and inflammatory or destructive, in the posterior part of the hypothalamus—by the interruption of the inhibitory nervous pathways which control the release *of hormones from the anterior pituitary*

Prophylaxis of Pulmonary Embolism

Dr N M Gibbs had investigated the relationship between venous thrombosis of the lower limbs and bed rest Thrombosis began in two separate and clearly defined sites—namely, the leg and the thigh—where venous stasis was particularly likely A simple apparatus had been designed which afforded complete control of exercise of leg and thigh muscles in patients confined to bed The "soleus ergometer" consisted of a pivoted platform attached to a spring of variable tension The platform was depressed by plantar flexion of the feet and each full movement of the platform was recorded on a meter The apparatus was mounted on an adjustable carriage clamped to the foot of the bed The spring tension and position of the apparatus may be adjusted with regard to height, age, and strength of the patient *An average of 30 recorded acts of plantar* flexion per hour during the waking hours was thought to be adequate in preventing thrombosis

Cytological Observations on Carcinoma

In their study of invasion of tissues by carcinomas, Dr R A Q O'Meara and Mr R D Jackson had applied standard cytological methods to fresh biopsy material Staining of the *Golgi apparatus* had shown different results in humans from those obtained by Ludford[1] in animals In squamous-cell carcinomas it was found that the arrangement of the Golgi apparatus in the normal epidermis corresponded to that found in carcinoma invading the tissues, in so far as the basal cells of the epidermis corresponded to the peripheral cells of invading carcinoma, and the mature cells of the epidermis undergoing keratinisation corresponded to those of the central parts of the carcinoma Thus, in squamous carcinoma, the tumour was maturing by mitosis and keratinisation towards the centre of the growth, while the peripheral cells of the carcinoma were growing outwards into the tissues in the opposite direction. It was found that the peripheral cells, when stained to show mitochondria, appeared to be forming fibrils, which were deposited on the outlying invading cells Sometimes the invading cells were overwhelmed by the deposit and they were then removed by phagocytes, for the most part they thrived and grew outwards into the deposit The fibrils could be found in advance of the main body of the tumour, forming a coagulum in the tissue spaces, thus interfering with the nutrition of the cells of the part and providing the carcinoma cells with an advantage

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[1] Ludford, R J *Quart J micr Sci* 1924, 69, 27

HEBERDEN SOCIETY AND DUTCH SOCIETY OF RHEUMATOLOGISTS

The Heberden round and a joint meeting of the Heberden Society and the Dutch Society of Rheumatologists were held at Leiden on April 25 and 26

Rheumatoid Arthritis and Pericarditis

Prof J Goslings gave the annual Heberden round at the University Hospital He described 13 cases of pericarditis and rheumatoid arthritis, 3 of which had come to necropsy Most of the patients had severe active rheumatoid arthritis, and some had other visceral involvement Several had the lupus-erythematosus (L E) cell phenomenon In 4 patients pericarditis had been recognised where the duration of rheumatoid disease had been less than eighteen months The clinical recognition of pericarditis might be difficult, physical signs might be transient and the electrocardiogram negative in cases showing pericarditis at necropsy Professor Goslings thought that this difficulty might explain some of the differences in the reported prevalence of pericarditis between patients and necropsy series

Incidence of Fractures

Dr S A Den Oudsten and Dr B Speyer (Rotterdam) had compared the frequency of spontaneous fractures of long bones and crush fractures of the spine in a group of adult patients with severe rheumatoid arthritis, with that in a control group of comparable non-rheumatoid invalids In both groups the age of the patient and the degree of immobilisation contributed significantly to the development of both types of fracture, but no significant difference could be found between the rheumatoid group and the controls Cortisone in the usual therapeutic doses did not seem to increase the incidence of fractures

Latex Fixation Test

Dr H A Valkenburg and Dr C A De Mos (Leiden) had used the 'Latex' fixation test of Singer and Plotz for the diagnosis of rheumatoid arthritis, with certain slight modifications including the use of a glycine buffer (pH 8 2) instead of a borate buffer, and a longer time between preparation and reading of the test A titre of 1 20 was taken as positive, and the test showed good reproducibility Serum samples from 1023 patients and controls were tested Of those with definite rheumatoid arthritis, 86% showed positive reactions, 83% of non-rheumatoid patients and 92% of the normal subjects gave negative reactions When the results were analysed in terms of strong reactions only, the proportion of non-rheumatoid positive reactions was reduced to 3 6%

L.E. Cells

Dr W Hijmans and Dr H R E Schuit (Leiden) discussed the L.E.-cell phenomenon In 2000 patients with various diseases they had discovered 200 positive cases, but only 1 of these positive cases could not be classified as belonging to the group of so-called collagen diseases The hypothesis (as yet unproved) that the L E cell was the result of an immunological mechanism had received strong support from many workers It seemed that nuclear protein, or a part thereof, but not desoxyribonucleic acid, could be regarded as antigen, and the L E -cell factor (a component of L.E globulin) as autoantibody They had shown that the L E -cell factor could react with the nuclei of calf thymocytes and of hen red blood-cells Even if phagocytosis were prevented, the typical "inclusion" bodies could be formed, though of course they were then free and unincluded, and therefore phagocytosis itself was not an essential part of the reaction They had shown that leucocytes would engulf nucleoprotein itself in the presence of L E factor

Leukæmia

Dr E Kruyff (Wassenaar) reported that of 1996 Dutch patients with ankylosing spondylitis treated with radiotherapy, in whom a follow-up rate of over 90% had been achieved, there had been 256 deaths, 25 of which were due to leukæmia or aplastic anæmia—thus confirming the increased incidence of leukæmia after radiotherapy, to which Van Swaay had called attention in 1950 Several instances of leukæmia in patients treated with deep X-rays for conditions other than ankylosing spondylitis had been reported The incidence of leukæmia was steadily rising in the Dutch population as a whole

Aspirin and Occult Blood

Dr L Th F L Stubbe (Leiden) had found occult blood, judged by a positive benzidine reaction, in the stools of about 70% of 180 persons (140 patients, 40 normal controls), to whom aspirin had been administered in tablet or powder form The phenomenon was reproducible in patients who showed it, and the alternation of aspirin with sodium salicylate was followed by the appearance and disappearance of the occult blood from the stools The amount of aspirin taken had little influence on the appearance of occult blood From the strength of the reaction, and from spectrophotometric determinations, it was shown that the positive benzidine reaction was indeed due to blood, and that up to 4 ml a day might be lost in this way This figure exceeded the normal blood-loss of menstruating women, and might be significant in the production of anæmia in rheumatoid arthritis

Reviews of Books

Applied Physiology of the Eye

The late H Willoughby Lyle, M D, F R C S, assisted by T Keith Lyle, C B E, M D, M R C P, F R C S London Bailliere, Tindall, & Cox 1958 Pp 342 45s

The physiology of vision is a subject seldom adequately presented to the undergraduate student, for it includes not only the whole of the processes involved in the formation of retinal images and their appreciation in the visual cortex but also those mechanisms concerned with the maintenance of the ocular circulation, metabolism, and pressure, and the neuromuscular apparatus of ocular movement This is one of the reasons why the average medical graduate finds difficulty in interpreting signs and symptoms of ocular disorder, and it accounts too for the relative seclusion of ophthalmology as a purely postgraduate specialty A textbook of applied physiology of the eye could do much to remedy this defect, and in the 22 chapters of this volume there is much that will enable the student and the aspirant to higher qualifications to interpret physiologically some of the visual disorders he sees

Anatomy must have a prominent place in the discussion of nervous mechanisms, and the fact that this part of the subject is treated descriptively rather than diagrammatically is responsible for its occupying the major part of the text in the chapters dealing with the ocular tissues and the cerebral structures associated with visual processes The parallel physiological explanation is lucid, and it is supplemented by reference to pathological conditions which provide a useful clinical background to the main description The selection of these pathological examples is perhaps in keeping with the eclectic character of the work as a whole, but it does not always contribute to the clinical perspective which the authors evidently seek The emphasis laid on encephalitis lethargica and the omission of tabes dorsalis as a cause of ptosis may be cited as a minor example of this, and the inclusion of episcleritis as the sole example of ocular collagen disease is another

The chapters dealing with cerebellar coordination, the thalamus and hypothalamus, and the VIIIth-nerve mechanisms form stimulating additions to the more purely ophthalmological parts of the text, but it is disappointing that so little space could be devoted to the visual tracts and the fields of vision The omission of any reference to the optical mechanisms of retinal image formation will also be missed by the ophthalmologist in training The short sections on ophthalmological eponyms and the Greek derivation of certain ophthalmological terms, however, form a welcome addition to the bibliography at the end of the book

The Handicapped and Their Rehabilitation

Editor HARRY A PATTISON, M D , F A C P , director of the Potts Memorial Institute, Hudson, N Y Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1957 Pp 944 *112s 6d*

THE rapidity of a patient's return to full activity after an illness once depended on the efforts of only two people—the patient himself and his doctor They will always be the two prime movers in reablement, but this new symposium from America draws attention to the number of allies whose assistance they may now profitably invoke Forty-four writers have contributed, nineteen of them medically qualified the others include physiotherapists, industrial psychologists, social workers, trade-union officials, a chaplain, and even a musician The editor suggests that the help of any or all of these ancillaries may be required to restore a patient to the complexities of modern life

Ten chapters relate to the treatment of particular illnesses (diabetes, tuberculosis, and cardiac diseases, for example), but most of them describe generally applicable rehabilitation methods, including some, such as music therapy and bibliotherapy, which have seldom been accorded separate consideration in this country A comparatively small part of the book is concerned with legislation and administrative details peculiar to the United States

Even allowing for the range of topics it describes, the book gives the impression that each chapter is addressed to a different audience Sometimes (as in the section listing technical faults in cleft-lip repair operations) that audience seems very specialised But many sections, such as an admirable one dealing with epilepsy, are of wide interest Though it does not deal with practical details, or the reablement of individual patients, the book discusses some problems, such as those posed by colostomy and by facial deformity, not mentioned elsewhere , and these sections will help many physicians and surgeons Moreover, in its entirety, the volume will help all those responsible for that coordination of the activities of many specialists which effective rehabilitation requires

The Mammalian Cerebral Cortex

B DELISLE BURNS, M R.C S , assistant professor of physiology, McGill University, Montreal London Edward Arnold 1958 Pp 103 *21s*

THIS monograph, which is the fifth in the present series sponsored by the Physiological Society, discusses only a few selected aspects of its title Those who know Dr Burns' work on the isolated cerebral cortex will not be surprised that this provides a central theme for the book "Isolated cortex" in this context refers to a slab of tissue from the surface of a cat's cerebrum which retains its pial blood-supply but has had all its neuronal connections severed The electrical properties of such preparations are described, and this provides a background for discussion of possible neurophysiological mechanisms which may be involved in activities like remembering and learning and in the interaction of different cortical areas The question whether or not spontaneous activity (here defined as the capability to discharge at moments not dictated by the precise times of arrival of energy from outside) is a characteristic of cerebral neurones is considered at some length without, however, any conclusion other than that the answer is not of immediate importance

Much of the ground usually covered in textbook accounts of the physiology of the cerebral cortex is omitted, but Dr Burns has succeeded well in his declared intention of writing for those "who do not operate oscilloscopes" about particular aspects of neurophysiology which intrigue him Readers whose curiosity is aroused by these topics will find plenty to hold their interest in this clearly written and adequately illustrated book

Polymyositis

JOHN N WALTON, M D , M R C P , first assistant in neurology, King's College, University of Durham, RAYMOND D ADAMS, M D , Bullard professor of neuropathology, University of Harvard Edinburgh and London E & S Livingstone 1958 Pp 270 *32s 6d*

THE authors review the group of disorders which includes dermatomyositis, scleroderma, generalised myositis fibrosa, relapsing myositis, and calcinosis universalis, and add 40 new cases of polymyositis of which 25 were seen by one or both authors They describe the clinical picture and differential diagnosis, paying particular attention to the points of distinction from muscular dystrophy, notably the presence of weakness of the neck muscles and sometimes of swallowing in polymyositis Skin lesions may be a valuable aid to diagnosis, but they are by no means necessary to the diagnosis The differential diagnosis is of importance because patients with polymyositis may benefit from corticoids The book is full of valuable references to the literature, but so much detail is given that it is not an easy book to read, and the salient features may be lost in detail

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Frazer's Anatomy of the Human Skeleton (5th ed London J & A Churchill 1958 Pp 247 50s)—Dr A S Breathnach's revision of Prof J E Frazer's classic will appeal to anatomists, and to surgeons training for the primary fellowship It is 18 years since the last edition, and much recent work on the development and growth of bone has been included. Dr Breathnach has, however, wisely maintained the original qualities of the book, which still offers the best text in descriptive osteology Frazer's illustrations remain largely untouched. Though not attractive in style, they are so clear and accurate in relating soft parts to bones that it would not be easy to improve them A few new drawings and, for the first time, radiographs have been added There has been some rewriting, and this has improved the text, we hope that it will be extended in later editions A wider bibliography would have made the volume more valuable to professional anatomists Like many texts of descriptive anatomy, it is parsimonious in functional interpretation of structure, and an addition of a few pages would invigorate and illuminate Old favourites like the arches of the foot are mentioned, but ribs are still chiefly a protection to viscera, we tour the orbit and leave it with no views on its functional appropriateness, the femur is long, but we are not told why If anatomists do not give some time to the significance of gross anatomy, who will ?

The Door of Serenity (London Faber & Faber 1958 Pp 119 21s)—This book by Dr Ainslie Meares describes and illustrates by a series of 24 coloured plates the stages of a lengthy and eventually satisfactory psychotherapy of a young schizophrenic girl Jennifer, as she is called, was 19 when first seen by Dr Meares, and the usual types of treatment proved unsuccessful She then began to bring him paintings, and over the next few years produced over 200 of these, from which he was gradually able to learn and interpret to her the root causes of her illness The book is not a complete or detailed case-history, but an outline of an interesting voyage of discovery undertaken by patient and therapist together

THE LANCET
LONDON 17 MAY 1958

American Reactions to the Staphylococcus

LIKE ourselves our American colleagues are worried by the high incidence of staphylococcal sepsis.[1] They note that reports of the same problem come from what they describe (apparently without intended irony) as "all medically advanced parts of the world". With characteristic energy and thoroughness, the American Medical Association, supported by sixteen other influential agencies, convened a conference of experts to discuss all aspects of the problem at Cleveland on Nov. 14, 1957. The essentials of the conference have now been published.[1,2] The experts remarked on the widespread dissemination throughout the hospitals of the United States and Canada of highly virulent, readily communicable, antibiotic-resistant strains of *Staphylococcus aureus* with a tendency to produce nasal carriers, skin lesions, wound sepsis, soft-tissue infections, and pneumonia. Neonatal infections and breast abscesses among nursing mothers were especially noted as troublesome to the sufferers and likely sources of spread of dangerous staphylococci to the general population. The conference thought that the situation arose from a tendency to relax the rigorous aseptic precautions which should be observed in hospitals and to rely instead on prophylactic administration of antibiotics. Vigorous investigation followed by rigorous measures often controlled infection in particular hospitals for the time being. Nevertheless, the conference considered that the troublesome hospital staphylococci had a special propensity for becoming resistant to a wide range of antibacterial agents, including leucocytes. It was on no less certain ground in proclaiming that we lack basic information about the ecology, pathogenesis, immune relationships, and variability of staphylococci —our knowledge of these matters being much poorer for staphylococci than for streptococci, pneumococci, and other pyogenic microorganisms. The conference recommended encouragement and money for research into these matters, and it suggested that every hospital should charge a responsible officer or committee with the investigation, control, and prevention of infections within the hospital. The whole community was advised to tackle the problem of spread of staphylococcal infection beyond hospitals through medical societies, local health departments, and inter-hospital committees on infections.

Of the need for some such actions there can be little doubt. How many hospitals in our own country are confident about the efficacy and safety of their sterilising and laundry procedures? How many provide clean air, or even abstain from doing operations and wound dressings in air that is richly charged with pyogenic bacteria? How many hospitals have effective procedures for checking whether members of staff with septic lesions on their persons are going about their duties and operating on, or otherwise attending to, patients whose tissues may have a lowered capacity to resist infection? In how many hospitals are junior medical staff or even nursing staff left to prescribe whatever antibiotics they happen to think might be useful? To what extent are antibiotics needlessly used as prophylactics in circumstances where the probability of sepsis is less than the risk of poisoning or sensitising the patient or producing another focus of antibiotic-resistant microorganisms? In practice, we regularly transgress in all these aspects of hospital routine. Defective sterilisers blow steam around without certainly producing sterile dressings. Laundries contaminate articles that were formerly free of pathogens. Hospital air is sucked from anywhere to anywhere else—even through the sterilised dressings inside sterilisers. Ward maids with pan and brush sweep rooms in which mothers put their infants to the breast. Nurses make beds immediately before or even during dressing rounds. Fluffy woollen blankets provide warmth scarcely needed in centrally heated hospitals; they cannot be sterilised or even very often washed without ruining them, and they fill the air with bacteria-laden dust. Nurses with boils on their noses remain on duty because they do not know the menace that they carry to their patients. Chiefs with an optimistic assurance that they have no trouble—whoever else may have it—leave instructions with sister to "give an antibiotic if it is needed". In the midst of all this, the bacteriologist may lecture, the superintendent may feel vaguely worried, the matron may consider that polishing is not enough, but—in the absence of flagrant disaster—nobody has power to act. Nobody, in all probability, even knows or can ascertain the exact rate of cross-infection in his own hospital. Probably things are at their worst in big hospitals with many separate units under distinguished chiefs. Disagreeable facts are not always revealed to the chief; to his eye all appears to go well. Terrible things, it is rumoured, happen downstairs and up above—but not here. And so the menace continues.

In considering which of the American proposals are applicable to our own situation, we hesitate to urge more sittings of committees or more committees. Many hospitals now have cross-infection committees. There should be one in every hospital, for its educative value may be considerable. But probably the general establishment of the post of hospital infection officer will have to be considered. Such a person should be senior in years and of consultant status. All infections, however trivial, should be reported to him, and he should see that they are properly investigated and the results recorded. He should be encouraged to go everywhere and probe everything that strikes his mind as possibly in need of investigation. He should systematically make the results of his work known to people concerned and to the medical and nursing staff as a whole. He should keep the administration in mind of its duty to provide a clean and wholesome hospital. Education and propaganda may accomplish some useful results, but they are not sure enough When it is important to ensure results responsibility must often rest with a single person That is why we now advocate the appointment as hospital infection officers of men of the highest professional and personal qualities This action has long been advocated by COLEBROOK,[3] and we believe that it is now required in order to control the increasing scandal of hospital cross-infections —a scandal which we seem unable to prevent by the gentle processes of self-education and self-discipline

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[1] Conference on Staphylococcic Infections. *J. Amer. med. Ass.* 1958, 166, 1177–1203; see also leading article, *ibid.* p. 1205.

[2] Ravenholt, R. T. *Amer. J. publ. Hlth*, 1958, 48, 277.

Extracorporeal Circulation

> " THE real key to further advance in the surgical treatment of established cardiac defects will only be provided by some simple and efficient method of maintaining the cerebral circulation while the heart is temporarily out of commission Naturally there are many other problems of a more local nature for solution but, so long as the surgeon is faced with the certainty of irreparable cerebral damage if he interrupts the circulation for any appreciable period, he has little incentive to devise operative procedures which can never be carried out "

THE late LAWRENCE O'SHAUGHNESSY wrote these words in 1939,[4] and they were repeated by Dr JAMES WATT, director of the National Heart Institute of the U S Public Health Service, in his opening address to the Conference on Extracorporeal Circulation in Chicago in September, 1957 O'SHAUGHNESSY recognised the ultimate need for extracorporeal circulation at a time when even closed operations on the heart were little more than a theoretical possibility He described some of his early experiments in animals with a perfusion apparatus, and clearly appreciated the essential part that was to be played by animal experiment

Following the work of a few pioneers in this country, in Sweden, and in the United States, the possibilities implicit in the successful application to man of the methods of extracorporeal circulation have been widely realised, and in the past three years a tremendous surge of enthusiasm has resulted in the cure of many patients During this period of development a vast quantity of experimental data—animal, biochemical, technological, and clinical—has accumulated and rival schools of technique were beginning to emerge In March, 1957, the surgical study section of the National Institutes of Health of the United States Public Health Service were asked by the National Advisory Heart Council to organise a conference on a world-wide scale to bring together workers in this field The conference, held in Chicago in September, was most successful, and a full report of its proceedings has just been published in this country[5]

Among all the scientific data may be found clinical results of great excellence J W KIRKLIN, for example, reports from a total of 245 cases no deaths due to perfusion in the last 39 patients and DE WALL from a slightly greater number of cases only 1 death from any cause in the last 40 patients, most of whom can be considered cured Such good results from these experienced workers were not obtained early in their series KIRKLIN reports 6 deaths in the first 10 patients and a further 6 deaths in the succeeding 27 While some of these early deaths could now be avoided even by the inexperienced, because the causes are becoming clear, it seems inevitable that such a complex procedure will continue to carry a high initial mortality Proper selection of cases will undoubtedly help to improve results, the selection of early cases is a grave responsibility for physician and surgeon alike

The general methods of perfusion and surgical technique are now established, and both apparatus and operative procedures are being constantly improved The goal of a really satisfactory oxygenator using diffusion of respiratory gases through a membrane is still distant, but it may have been brought a stage nearer by the report from Dr MELROSE and his colleagues on p 1050 The difficulties are partly mechanical (namely, in providing a surface area of membrane comparable to that in the human lung) and partly physiological (namely, in securing a material for the membrane which is innocuous to blood, is readily sterilised, and has the necessary diffusion characteristics for respiratory exchange)

It is becoming increasingly apparent that progress in this field is expensive The National Advisory Heart Council in the United States has approved grants of over $700,000 for future use in research on extracorporeal circulation, and this is over and above money derived from the universities and private benefaction In this country funds for research have been derived principally from the universities and from the Nuffield Foundation, but, with the reliability of oxygenators established, the main charge should fall henceforth on the National Health Service The need now is for a few teams, well supported technically, working constantly together clinically and in the laboratory

Modified A I D.

THERE has lately been heightened interest in the legal and moral issues raised by artificial insemination with donor's semen (A I D) for solving the problem of the childless couple where male infertility is the cause Clearly A I D is open to weighty objections, and any alternative method deserves careful consideration At the Hadassah University Hospital in Jerusalem Dr S ROZIN has been testing a modified technique of artificial insemination[6] ROZIN obtained semen samples from infertile husbands and separated the spermatozoa from the plasma The spermatozoa were then suspended in plasma obtained similarly from a normal donor's semen Five women of childless marriages were inseminated with their husband's spermatozoa suspended in this way and two of them became pregnant Firm conclusions obviously cannot be based on such limited figures, but ROZIN's idea merits some discussion

Successes with this method would be open to at least two explanations—namely, that donor spermatozoa were accidentally included in the material used for insemination, or that abnormality of the plasma of the infertile semen impaired the normal function of the spermatozoa Complete removal of spermatozoa from semen by centrifugation is remarkably difficult Centrifugation sufficient to produce a dense pellet of spermatozoa and other particulate bodies at the bottom of the tube may still leave actively motile spermatozoa suspended freely in the supernatant plasma The presence of these cells may go unsuspected, for the dilution of the spermatozoa is so extreme that their detection under the microscope requires patient examination It is reasonable to suppose that the spermatozoa that remain suspended in the plasma are there chiefly because they were among the most actively motile cells in the sample population Centrifugation may therefore have selected the most vigorous and presumably potentially the most fertile spermatozoa of the donor's semen, and their presence would constitute a very special hazard if the plasma were employed by ROZIN's method Abnormality of the plasma of infertile semen might manifest itself as a deficiency of some normal component, but it is most unlikely that lack of a normal constituent per se could underlie failure of spermatozoa to initiate conception, for pregnancy can be obtained by inseminating spermatozoa recovered from the epididymis and suspended in physiological-saline solution[7] On the other hand, deleterious effects on spermatozoa may conceivably result from gross imbalance of plasma composition, from a normal plasma constituent in abnormally high concentration, or from a foreign toxic substance in the semen These possibilities are largely hypothetical, and much work is still needed to establish their occurrence and practical significance

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[3] Colebrook, L *Lancet* 1955 ii 885

[4] *ibid* 1939 ii 969

[5] Extracorporeal Circulation (edited by J GARROTT ALLEN) Springfield Ill Charles C Thomas Oxford Blackwell Scientific Publications 1958 Pp 518 57*s* 6*d*

[6] See N Y *Times*, April 14 1958

Many observations have been made on conditions affecting spermatozoa in vitro[8], and it is known that they are, on the whole, more resistant than most body cells to changes in physical and chemical environment Motility is, of course, abolished if conditions depart sufficiently from normal, and it is reduced by metabolic enzyme inhibitors Usually spermatozoa recover their motility if removed from the medium containing the inhibitor before too long a time has passed and are placed in a medium lacking inhibitory effect Recovery occurs perfectly well in artificial media, and therefore does not depend on the presence of any constituent of the male accessory secretions Broadly speaking, fertility is correlated with motility[9 10] Generally, fertility is lost before motility, and PARKES[11] and PARKES et al[12] have shown loss in this order to be especially constant following the use of certain enzyme inhibitors, which remove fertility without greatly affecting motility WERTHESSEN et al,[13] in a study of seminal properties and fertility in stud stallions, exchanged the spermatozoa and the seminal plasma of several animals and noted that the plasma of different animals differed in its capacity to maintain spermatozoon motility Maintenance of motility was inversely correlated with the concentration in the plasma of non-protein sulphydryl compounds, which evidently exerted a deleterious influence on the spermatozoa Further investigations showed that fertility also was inversely associated with the concentration of these compounds Finally, the investigations were extended to man, and here again the concentration of non-protein sulphydryl compounds, though much lower than in stallion semen, was inversely correlated with motility maintenance WERTHESSEN et al infer, therefore, that in man, too, the sulphydryl concentration may be inversely related to fertility

Thus in the human male infertility may sometimes be due primarily to abnormality of the seminal plasma, and this abnormality may possibly take the form of unusually high levels of non-protein sulphydryl compounds If this were proved to be so, remedial measures would involve removal of the spermatozoa from their native plasma Insemination would require resuspension of the spermatozoa in another medium, but this need not necessarily be seminal plasma unless the damage suffered by the spermatozoa could be repaired only by a specific factor in normal semen Meanwhile much further research is clearly needed

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[7] Hanley H G Stud Fertility 1956 8 20
[8] Mann T The Biochemistry of Semen London 1954
[9] Bishop M W H Campbell R C, Hancock J L Walton A J agric Sci 1954 44 227
[10] Bishop M W H Stud Fertility 1955 7 48
[11] Parkes A S Lancet 1953 ii 1285
[12] Parkes A S Rogers H J Spensley P C Stud Fertility 1954, 6 65
[13] Werthessen N T Marden W Haag I, Goldzieher, J W ibid 1956 8 12

Annotations

A NEW AUSTRALIAN MEDICAL SCHOOL

IT is exciting to contemplate the long-overdue rebuilding of some of the medical schools in this country—for example, at Liverpool, as we report on p 1066 But how much more exciting to welcome a completely new school! Men and women of Western Australia wishing to study medicine have had to leave their home State, usually for Adelaide, for the preclinical and clinical years, and in 1955 the Government decided to establish a medical school at Perth—provided that the university could show that public opinion was in favour by the stringent test of raising £400,000 by appeal (the population of the State is less than 700,000) The result of the appeal was unequivocal, for more than £500,000 was subscribed, and plans for a new school were begun, and on April 10 Sir Charles Gairdner, the Governor, formally opened it.

The faculty of medicine is the ninth in the university Teaching began with the academic year in 1957, when a first-year class of 85 students was enrolled, and 16 Western Australian students who had been studying at Adelaide began their sixth-year work at Perth The departments of anatomy, physiology, and biochemistry began teaching in March

The school buildings are not yet complete, but more interesting than the prospects of new buildings are the prospects for teaching and research In designing its teaching programme the new school is doubly free, for not only has it no traditional curriculum but also it begins work at a time when the General Medical Council has relaxed its detailed control and permits experiments Until 1957 the Council had been precise and detailed, and while its influence had certainly maintained an adequate standard of education in English and Australian medical schools, it had tended to stifle individual enterprise in the framing of new forms of teaching or new approaches to the medical curriculum " Today the staff have an opportunity for boldness For research there is ample money available, since, besides several bequests made in the years before the appeal and a gift to establish a research foundation (primarily for investigation of cardiovascular disease), £250,000 of the appeal moneys has been set aside for research and special projects, and the balance, beyond the sum needed to establish the school, has been used to form a permanent endowment fund We send our greetings and good wishes to all concerned in the new school

HYPERTENSION DUE TO RENAL-ARTERY STENOSIS

ANY lesion which significantly narrows a renal artery may induce hypertension This type of hypertension is important particularly because it may be relieved by restoring an unobstructed blood-flow to the kidney, or by nephrectomy if the disease is unilateral[1] It has long been recognised that such conditions as unilateral atrophic pyelonephritis may be associated with reversible hypertension, but that stenosis of the main renal artery can cause increase of blood-pressure has become apparent only in the past few years A renal humoral mechanism, similar to that demonstrated by Scott and Bahnson,[2] in thoracic coarctation of the aorta, is thought to be responsible Hypertension due to unilateral renal arterial stenosis differs, however, from that due to coarctation in that the contralateral kidney is exposed to the full effects of the disease

Although few instances of hypertension associated with renal-artery stenosis have been reported, a surprising variety of lesions has been noted in young people congenital stenosis and other anomalies of the renal-artery, aneurysm of the renal artery, and coarctation of the abdominal aorta, in older patients atherosclerosis, trauma, compression, thrombo-angiitis, and embolism of the renal artery

The symptoms and signs of this type of hypertension are unfortunately no different from those of other types the diastolic level is high and stable, and signs and symptoms progress rapidly Diagnosis is therefore not easy and depends essentially on arteriography It would obviously be unwise and unnecessary to subject every hypertensive patient to renal arteriography, and much judgment is needed to select patients for this elaborate investigation DeCamp and Birchall[3] advise arteriography in all patients whose hypertension develops (in the absence of primary renal disease) before the age of 25, and in all in whom persistent severe diastolic hypertension comes on after the age of 50—similar recommendations to those of Poutasse and Dustan[4] In the intervening age-groups they undertake aortography if there is something in the history which does not conform to the normal pattern of essential hypertension It is important to exclude as far as possible a phæochromocytoma before aortography, as the injection may provoke a fatal hypertensive attack In the adult aortography is performed by translumbar puncture of the aorta just above the mouths of the renal arteries if placed too high the dye escapes into the other major aortic branches and the renal vessels are not plainly seen In children the dye may be put in retrogradely by catheterisation of the femoral arteries

Adequate renal circulation may be restored by excising the strictured area and reconstructing the artery by end-to-end suturing, by endarterectomy, or by using the splenic artery as an end-to-side anastomosis DeCamp and Birchall[3] believe that, with arteries of the size of the renal, free grafts (homografts or synthetic) are best avoided Freeman[5] followed three cases in which the renal artery was occluded during endarterectomy for aortic thrombosis, the grumous material being accidentally forced into the orifice of a renal artery In one of the patients severe hypertension developed but subsided after nephrectomy

Aortography during investigation of high blood-pressure would be advised more commonly if the technique was free of complications Huger et al[6] have attempted to minimise the risk of renal parenchymal damage, during the flooding of the kidney with dye, by giving an intra-aortic injection of procaine before the dye There is evidence that in dogs this gives some protection, but in man this is less clear, and two other factors are much more important—the site of injection and the dose of contrast medium The constant factor in reported cases of severe bilateral renal damage has been the large dose of concentrated organic iodide used Renal arteriography should be done with 30 ml or less of one of the less toxic dyes, such as sodium diatrizoate (' Hypaque '), with such a quantity the risk of parenchymatous damage is very slight

THESAUROSIS

ANOTHER foreign body is being added to our reticulo-endothelial system's treasure chest Bergmann et al[7] report the case of a 27-year-old receptionist who had mild malaise and increasing fatigue for two or three months and was admitted to hospital with a chest radiograph which showed bilateral fuzzy hilar enlargement and reticulated infiltration of all parts of both lungs A general examination six years before had included a chest radiograph, which had been entirely normal Physical examination and many tests all yielded normal results except for the chest picture Resection of the right scalene fat pad produced three moderately firm lymph-glands, one of which yielded no organisms on a wide variety of cultures Histological examination of the other two showed pronounced hyperplasia of large epithelioid cells with occasional giant cells Again no organisms could be found, nor was there any fat in the cells of the granulation tissue There were, however, round granules in the epithelioid cells and interstitial tissue The only foreign body which could be incriminated was a hair-spray which the patient had used for two years, during the last six months of which her hair had been sprayed twice daily After the use of the spray was stopped, radiographs of the chest showed partial clearing of the infiltration and lymphadenopathy in two months and a normal picture after four months Shortly before this, a 22-year-old married woman had been seen as an outpatient because of an abnormal chest radiograph found on routine examination there was extensive bilateral reticulated infiltration of both lung fields and enlarged lymph-nodes in both hilar regions, but the patient was in good health and denied any respiratory symptoms A pre-employment radiograph two years earlier had been normal When nothing else could be found to account for the conditions, the patient was asked about inhalants She had used a hair-spray almost daily, sometimes twice a day, for about three years Two months after stopping the use of the spray, radiography showed regression, and another month later the picture was virtually normal

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[1] See *Lancet* 1956 ii 562 *ibid* Jan 25, 1958 p 201

[2] Scott H W Jr Bahnson H T *Surgery*, 1951 30 206

[3] DeCamp P T, Birchall R *ibid* 1958, 43, 134

[4] Poutasse E F Dustan H P *J Amer med Ass* 1957, 165, 1521, see *Lancet*, Jan 25 1958, p 201

[5] Freeman N E Leeds F H, Elliott, W G, Roland S I *J Amer med Ass* 1954 156, 1077

[6] Huger, W F, Jr Margolis, G Grimson K S *Surgery* 1958 43 52

[7] Bergmann M, Flance I J Blumenthal, H T *New Engl J Med* 1958, 258, 471

These stories seem simple in retrospect, but consternation was caused by the discovery of an apparently serious, widespread infiltrative process in the lungs in supposedly healthy young women Bergmann et al could not determine the exact nature of the particulate matter found in the lymph-glands in the first case They evaporated to dryness 20 ml quantities of hair-spray, suspended the residues in saline solution, and injected the suspension subcutaneously into guineapigs One to two months later the sites of injection showed granulomatous lesions in which particulate matter was found in foam cells, and similar granules were found sometimes in liver, spleen, or lung The reaction was typical of the macromolecular substance reaction[8] given by the various natural and synthetic resins used in cosmetics as well as for many other purposes While most of these substances are chemically inert, and relatively large quantities may be stored in the reticulo-endothelial system without affecting function, there is always the possibility that one may be carcinogenic[9], and the diagnostic difficulties to which they may give rise should be generally recognised

DETERMINING PROTEINS IN LOW CONCENTRATION

THE most accurate methods for determining the relatively small amounts of protein that may be present in biological fluids, such as urine and cerebrospinal fluid, involve either gravimetric estimation after precipitation, or estimation of the nitrogen content of the precipitated and washed protein by the micro-Kjeldahl technique But these methods are time-consuming and thus unsuitable for use in busy routine laboratories All the methods in routine use sacrifice, to some extent, accuracy for speed They depend either on estimation of the volume of the precipitated protein, as in the unsatisfactory Esbach method, or, better, on precipitation of protein and comparison of the resulting turbidity with turbidimetric standards, or, better still, on comparison of the colour developed in the biuret reaction with that developed by a standard biuret or standard protein solution This last method usually gives an answer within 5% of that given by a micro-Kjeldahl technique[10] The error of the turbidimetric methods is usually less than 10%, but occasionally may be as high as 20%[11] The Esbach method may give results varying from half to twice the true amount[12]

Closs[13] has described a new reagent for precipitating urinary proteins, which are then determined turbidimetrically in a photoelectric colorimeter The reagent is an 0 2% solution of sodium polythionate brought to a pH of about 2 1 ml of urine is mixed with 10 ml of reagent in the cold, and the turbidity produced after 30 minutes can be assessed qualitatively or estimated quantitatively The reagent is made freshly each week from a stock solution, which will keep indefinitely at room-temperature Closs finds that, qualitatively, the method is as sensitive as Heller's test, which will detect 7 mg of protein per 100 ml[14] Quantitatively the method, applied to urinary protein, appeared to agree somewhat more closely with the micro-Kjeldahl technique than is usual with turbidimetric procedures Its usefulness in determining the protein content of other biological fluids has yet to be ascertained

This method has certain small advantages, in that the amount of fluid required is 1 ml or less, the degree of dilution reduces the error that may arise with initially turbid urines, no heating is necessary, and interfering precipitations or colorations are rare

SURVEY OF CHILDREN

IT is a matter of common clinical experience that infants and children from poor homes do not thrive as well as the socially better favoured But the precise effects of social conditions on physical and mental health and development are not easily defined A study by Douglas and Blomfield[15] provides much long-awaited material

The starting-point of the work was the investigation by the Population Investigation Committee and the Royal College of Obstetricians and Gynæcologists into the circumstances and costs of all confinements in Great Britain during the first week of March, 1946 Of the 14,000 families involved in that inquiry[16] 5000 children were selected for longitudinal study, and it is their life-stories up to the age of 5 that Douglas and Blomfield are now concerned with

These children spent their early years in the unsettled post-war era and have been subject to the manifold social changes of the time, not least of which was the inception of the National Health Service when they were 2 During the survey period (1946–50) housing conditions steadily improved, and many of the families moved upward in the social scale This background has to be remembered in assessing some of the findings of the survey, or in extrapolating conclusions for present-day needs

Poor social conditions showed differing effects according to the age of the child In the perinatal period such conditions were associated with an increase in prematurity and neonatal death, in infancy with early and severe respiratory infections, and in childhood with significant depression of growth At all ages the direct cause of socially determined disorders was "maternal inefficiency" with poverty, overcrowding, and large families appearing as predisposing factors The report shows clearly that successful mothering of a large family, where the housing conditions are poor and the budget is slender, requires care, resourcefulness, education, and supportive advice The best showing was made by the families of "black-coated workers" As a group they are not materially better favoured than skilled workers, but by care, ability, and utilisation of child-welfare services they achieve not only favourable development for their children but also often fulfilment of their social aspirations

Douglas and Blomfield feel that "the social and educational approach" offered by the local-authority child-welfare services has done much to improve standards of maternal care, and that this is " still of primary importance in the saving of infant life " They urge that the existing services be retained, with some reorganisation, saying that the time is not yet ripe for their disbandment But it must be noted that in the survey material the incidence of fatal illness was highest before treatment by family doctors became available to all without fee under the N H S , that the incidence of infections (without regard to severity) in all but the highest social groups was no lower among the " careful " mothers, and that schoolchildren and chronically infected adults were important spreaders of family infections Moreover, the infant-welfare clinics failed to attract the mothers most in need of their services

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[8] Hueper W C *Arch Path* 1942 33 267
[9] Hueper, W C *Cancer* 1957, 10 8
[10] Hiller, A Greif, R L, Beckman W W, Plazin, J *J biol Chem* 1948, 176 1421
[11] Varley, H Practical Clinical Chemistry London 1954
[12] Peters J P, Van Slyke D D Quantitative Clinical Chemistry, vol 2 London 1932
[13] Closs, K *Scand J clin Lab Invest* 1957 8, 349
[14] Harrison G A Chemical Methods in Clinical Medicine London, 1957
[15] Children Under Five By J W B DOUGLAS and J M BLOMFIELD London Allen & Unwin 1958 Pp 177 21s
[16] Maternity in Great Britain London 1948 See *Lancet*, 1948, ii 813

Other matters no less important are illuminated by the study The possible ill effects of separation, family breakup, and the employment of mothers were investigated Although the inquiry was necessarily superficial, no convincing evidence appeared that these had any adverse effect on the physical or emotional wellbeing of the children There was some suggestion that when the separation involved admission to hospital neurotic symptoms increased Victims of accidents tended to be superior children, indicating the inevitable risks incurred by those with a healthy body and adventurous spirit The findings on toilet-training confirm the impression that girls more quickly acquire continence than boys Enuresis is strongly associated with poor maternal care, and early pot training within a secure home is followed by the most rapid attainment of sphincter control This is contrary to the often-expressed view that early potting is a manifestation of coercive training likely to be followed by failure and neurosis

The Institute of Child Health (University of London), the Society of Medical Officers of Health, and the Population Investigation Committee are to be congratulated on sponsoring this study It is good news that the Nuffield Foundation have made a grant to enable the study to continue until the children reach the age of 15

THE BONE CRYSTAL COMPLEX

PROGRESS in work on the structure of bone has been reviewed by McLean[1] The histological unit is the osteon—the Haversian system with canal, concentric bony lamellæ, cells, and canaliculi—150 µ in diameter and several millimetres in length Throughout adult life there is a constant process of " Haversian remodelling " of compact bone, at any given time a certain amount of labile reactive bone—about 1% of the total mass of bone—is present, and it is this 1%, actively exchanging substance with the surrounding tissue-fluids, that makes bone a living and not a dead material The organic unit of bone is the collagen fibril—800Å made up of macromolecules secreted by the osteoblast The inorganic unit is the rod-shaped bone crystal—$3Ca_3(PO_4)_2\ Ca(OH)2$, hydroxyapatite—about 200Å long and 75Å in diameter The crystals are oriented in the long axis of the collagen fibril and packed round the region of the periodic cross-banding, leaving uncovered gaps along the fibril[2] Owing to their minute size the crystals have an enormous surface-area per unit of mass—of the order of 200–300 sq m per gramme It is thus expanse of crystal surface that gives bone its most important non-mechanical function—the " homeostatic regulation of the ionic composition of the circulating fluids of the body, and a reservoir of th calcium ion "[3]

Around each crystal, and partly bound to its surface, a layer of hydrated ions together with a " shell " of wate Each gramme of crystal, it is claimed, can hold 0 8 g of water in this way, and so there is a greater volume o water than crystal Any ion from the surrounding flui can diffuse into the water shell The layer of hydrate ions—calcium, phosphate, and hydroxyl—is constantl exchanging with similar ions in the surface layer of th crystal lattice, and there is a much slower ionic interchange between the surface and the interior of th crystal Of the ions circulating in the body-fluids K^+ and Cl^- can penetrate only as far as the hydration shell Na^+, UO_2^{++}, CO_3^{--}, and citrate^{---} can displac calcium phosphate or hydroxyl ions from the crystal lattic surface, while Ca^{++}, Sr^{++}, Ra^{++}, PO_4^{---}, and F^- ca penetrate into the interior of the crystal structure Such ionic movements take place wherever body-fluids are i contact with the crystal complex of reactive bone As the crystals age and increase in number, they displace th water and so become dehydrated and inert like natura mineral deposits

Some quantitative data on interchange of ions between blood and bone have been obtained by means of radioactiv isotopes such as ^{45}Ca, ^{32}P, and more recently ^{47}Ca External counting gives approximations of the magnitude and rate of this exchange For instance, it is known that in young animals the total calcium in the blood (10 mg per 100 ml) is replaced,every minute

Equilibrium between the blood and the reactive bone of the mineralising osteon is maintained by constant adjustment through ionic interchange between bone, extracellular fluid, and serum This immediate control mechanism may, it is believed, also involve bone-cell activity, with the formation of citric acid, which acts as a carrier and conveys calcium from bone to blood-stream The level of citric acid in bone is influenced by parathyroid and vitamin D[4]

In addition to the minute-by-minute regulation the parathyroid glands are essential for the maintenance of the plasma-calcium at the physiological level of 10 mg per 100 ml If the parathyroid glands are removed the calcium level falls to 7 mg per 100 ml , and with parathyroid hyperactivity it may rise to 15 mg per 100 ml Parathyroid reaction to changes in calcium-ion concentration is effective in terms of hours, compared to the more immediate results of ionic transfers, and is brought about by the dissolution of mineral from the stable bone—probably by the activity of mobilised osteoclasts[5]

More work on the electron microscopy of bone is required—particularly with regard to the disposition of the bone crystals, the fine structure of the ground substance, and the study of radio-isotopes at the level of ultrastructure

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Dr DEREK STEVENSON has been appointed secretary of the British Medical Association in succession to Dr ANGUS MACRAE, who reaches retiring age in November Dr Stevenson has been a deputy secretary since 1948

The next session of the General Medical Council will open on Tuesday, June 3, at 2 15 P M , when Sir DAVID CAMPBELL, the president, will deliver an address The Medical Disciplinary Committee will meet on Wednesday, June 4, at 11 30 A M

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Public Health

SMALLPOX IN TOTTENHAM—1957

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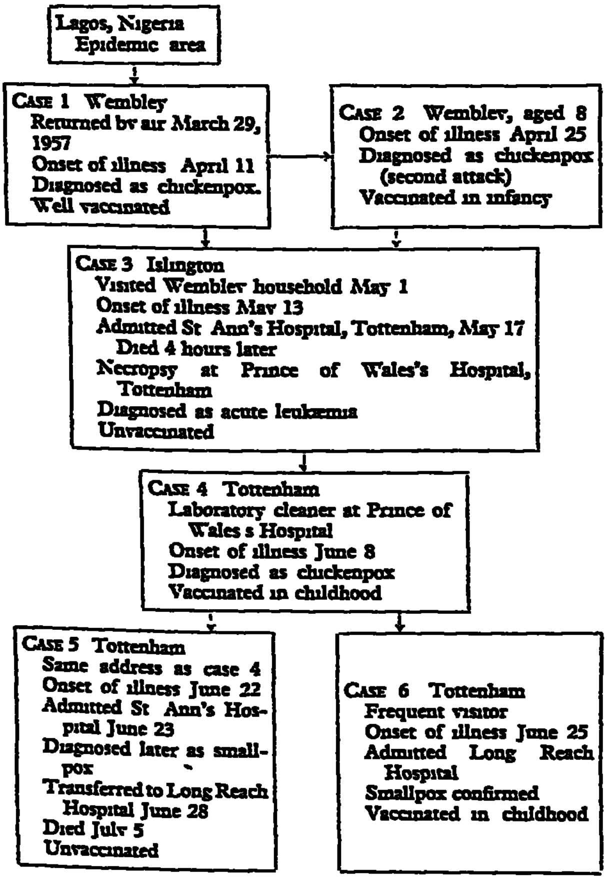
LOOKED at in retrospect and in the accompanying graphic chart, the smallpox outbreak in Tottenham in the summer of 1957 appears small and neatly disposed of as an epidemiological study This does not mean, however, that the incident was not a full-scale exercise in accepted methods of investigation and control, or that it was without clinical, social, and administrative features of special interest. What may not be so easy to explain is why the disease did not spread more widely despite the measures taken



Lagos, Nigeria
Epidemic area

CASE 1 Wembley
Returned by air March 29, 1957
Onset of illness April 11
Diagnosed as chickenpox.
Well vaccinated

CASE 2 Wembley, aged 8
Onset of illness April 25
Diagnosed as chickenpox (second attack)
Vaccinated in infancy

CASE 3 Islington
Visited Wembley household May 1
Onset of illness May 13
Admitted St Ann's Hospital, Tottenham, May 17
Died 4 hours later
Necropsy at Prince of Wales's Hospital, Tottenham
Diagnosed as acute leukæmia
Unvaccinated

CASE 4 Tottenham
Laboratory cleaner at Prince of Wales's Hospital
Onset of illness June 8
Diagnosed as chickenpox
Vaccinated in childhood

CASE 5 Tottenham
Same address as case 4
Onset of illness June 22
Admitted St Ann's Hospital June 23
Diagnosed later as smallpox
Transferred to Long Reach Hospital June 28
Died July 5
Unvaccinated

CASE 6 Tottenham
Frequent visitor
Onset of illness June 25
Admitted Long Reach Hospital
Smallpox confirmed
Vaccinated in childhood

Foremost in the experience gained was the sense of close cooperation which existed from the moment the first case was suspected, and remained throughout subsequent events, between the Ministry of Health, the North East Metropolitan Regional Hospital Board, the Virus Reference Laboratory, Colindale, the members of the panel of smallpox opinion, local hospitals' medical and administrative staffs, general medical practitioners, and the medical officer of health's department.

The Early Stages

By telephone at 10 15 A M on Friday, June 28, 1957, the medical officer of health (G H H) was informed by the consultant physician for infectious diseases (G D McK) at St. Ann's General Hospital, Tottenham, of a case of suspected smallpox in that hospital

An unvaccinated boy aged 6 (case 5), had been admitted to the poliomyelitis unit of the hospital on June 23 with a history of backache, fever, abdominal pain, and vomiting On admission he was ill, with abdominal tenderness and guarding, and a temperature of 102°F He had general ichthyosis and superimposed patches of eczema The practitioner's provisional diagnosis of poliomyelitis was not borne out by this further examination, which suggested an acute abdominal emergency At laparotomy the appendix (which was removed) was found to be normal, but the mesenteric glands were seen to be enlarged During the next three days the patient remained febrile and ill, and there was some bleeding around the abdominal wound On admission a few macules had been noted in the interscapular area, and by June 27 it was evident that he had a rash, predominantly papular and peripheral, besides the chronic skin condition. At the time eczema herpeticum was thought to be more likely than smallpox, but skin scrapings and fluid from one or two vesicular lesions were sent to the Virus Reference Laboratory, Colindale

Next morning there was a striking change in the child's appearance The rash was vesicular and becoming confluent, and smallpox could be confidently diagnosed on clinical grounds Following the telephoned report of these facts to the medical officer of health, an immediate consultation was held at the hospital, when it was agreed to call in a second member of the panel of smallpox opinion (Dr A M Ramsay) and to report the situation by telephone to the principal medical officer of the epidemiology division of the Ministry of Health (Dr W H Bradley) Before noon both Dr Ramsay and a medical officer from the Ministry (C G N) had arrived at the hospital and agreed to the clinical diagnosis of smallpox Arrangements were made for the immediate transfer of the patient to Long Reach Hospital, Dartford, under the care of the late Dr M Mitman During the same day a preliminary report was received from the director of the Virus Reference Laboratory (Dr F O MacCallum) that the complement-fixation test was strongly positive for variola-vaccinia On July 5 the boy died Throughout his stay at St Ann's Hospital he had been barrier-nursed in single cubicles—for the first four hours in the poliomyelitis unit and for the remainder of the time in another cubicle block

Before the clinical diagnosis had been confirmed, his parents had been interviewed by the chief public health inspector (Mr E T Jenkins) and detailed information of the members of the household and their occupations obtained The father, a bus conductor, had reported at his depot that morning, since this was an obvious risk the medical officer of health at once spoke on the telephone to the chief medical officer of the London Transport Executive

This early inquiry into the home circumstances revealed a further case of smallpox, the boy's grandmother (case 4) living in the same house and by this time convalescent

This patient, vaccinated in childhood and now aged 61, had fallen ill on June 8, a rash (which was thought by her doctor to be that of chickenpox) developed on June 12 She was seen by two of us (G H H and C G N) in consultation with Dr Ramsay The clinical findings were equivocal but consistent with a modified attack of smallpox In view of the satisfactory vaccinal state of the rest of the household, now refreshed by further vaccination, it was considered justifiable to await the result of laboratory examination of scrapings taken from the most suitable of the few remaining lesions To complete this patient's subsequent history, the complement-fixation test was reported as positive on the following day, when she was removed to Long Reach Hospital, and a positive egg culture was reported as further confirmation two days later This patient continued an uninterrupted convalescence and was in due course discharged from hospital

From the chief public-health inspector's inquiries, it was learned that the patient was employed as a domestic worker in the pathological laboratory at another hospital in the Tottenham group of hospitals—a circumstance which it was felt must afford some explanation of her infection (This matter is referred to later in the account of the outbreak)

ACTION TAKEN AT ST ANN'S HOSPITAL

It was agreed that immediate responsibility for vaccination and other control measures at St Ann's Hospital should be undertaken by one of us (G D McK) who had arranged for the supply of enough lymph to vaccinate the whole complement of the hospital, and for the preparation of a list of all primary contacts on the staff with their vaccinal history and that of the other patients on the two wards in which case 5 had been nursed

There were 42 primary contacts among the staff and 31 patients in the two wards, only 6 of the patients had been vaccinated Permission to vaccinate these children was sought by telegram and all but 2 were vaccinated within twelve hours—the remaining 2 being vaccinated next day when permission was received

When we discovered the inadequate vaccinal state of the children nursed in the cubicles adjacent to case 5, we decided to give them hyperimmune anti-variola gamma-globulin forty-eight hours after vaccination, and accordingly these 15 children each received 5 ml All 42 primary contacts among the staff had been vaccinated at some previous time, but in 9 there was no satisfactory proof of recent *successful* vaccination, and each was therefore given 10 ml of hyperimmune gamma-globulin Our findings agree with the observation of Kempe et al (1956) that administration of hyperimmune gamma-globulin (twenty-four hours after vaccination in their series) does not interfere with the course of vaccination, for all 24 of our vaccinations were successful Vaccination of the remaining hospital patients and staff (about 1000 persons) was started on June 29, and continued throughout the early part of the following week, revaccinations being done where necessary

The hospital was closed for admissions and discharges on Friday morning (June 29) and visiting was restricted to those seriously ill During the weekend a zone of isolation was set up (on the " hospital within a hospital " principle) using one previously empty ward, which was made into living quarters, and the two wards where case 5 had been nursed This area was roped off, and all 26 primary contacts among the resident staff of the hospital were isolated within it Entrance was restricted to the infectious-disease physicians, the senior administrative nurses, physiotherapists, and engineers Protective clothing was worn (cap, mask, gown, and boots) Food was supplied in destructible containers and all combustible material was removed to the incinerator in bins on a trolley reserved for the purpose

On July 1 a further ward was prepared to receive staff with vaccination reactions and doubtful illnesses requiring isolation and investigation This proved a valuable adjunct, and during the fourteen days it remained open 8 patients were admitted

St Ann's is a general hospital of 520 beds, of which 120 form an infectious-diseases unit There is normally considerable interchange of staff both between this unit and other departments and between the hospital and the other hospitals in the group By re-allocation of duties it was readily possible to avoid or reduce such interchange to the minimum, but the situation within St Ann's Hospital of the central laundry for the whole group gave rise to much concern It was found that no articles used by case 5 had been sent for laundering, and it was therefore decided to maintain the existing laundry services, save that the zone set aside for smallpox contacts would be provided with a washing-machine for each ward

No material therefore left the smallpox zone, except that destined for the incinerator

The closure of the group laundry would have caused considerable disruption in the work of all the contributing hospitals—so much so that the group laundry manager (Mr C H Adams) subsequently followed up the matter elsewhere, with the cooperation of one of us (C G N), and we understand that military mobile laundry units of varying capacities can be hired to meet such an emergency

It seems that the precautions were adequate, for there was no secondary case in the hospital or within the group, and with the uneventful effluxion of the sixteen days' surveillance it was possible to determine all isolation measures on July 15

Public-health Action

Reporting of Outbreak

During the afternoon of the first day, an official telegram was sent to the Ministry of Health confirming the earlier telephone message, the county medical officer was notified, the senior administrative medical officer of the North East Metropolitan Regional Hospital Board was informed of the position, and a circular letter (thereafter issued daily) stating the situation was sent to all general medical practitioners in the borough and to medical officers of health in adjoining local authorities The chief medical officer of the Ministry of Health notified all medical officers of health in the country and port medical officers of the progress of the outbreak by circular letters issued on June 28, July 1, and finally on July 5

Contacts of Case 5 before Admission to Hospital

Case 5 had been attending school until Friday, June 21 The school was visited before closure for the weekend, and duplicate registers and names and addresses of staff were obtained for purposes of offering vaccination or revaccination A list of recent visitors to the patient's home was prepared, including relatives, friends, neighbours, and tradesmen A list of patients since conveyed in the same ambulance was obtained from the local depot Arrangements were made with the Central Public Health Laboratory, Colindale, for the supply of 2000 capillary tubes of calf lymph for immediate vaccination or revaccination of primary contacts and the staff of the health department

Public Relations

On Saturday, June 29, a joint statement was issued to the Press by the hospital and public-health authorities

" In view of the suspected case of smallpox transferred from St Ann's General Hospital on the 28th June, the hospital has ceased to admit or discharge cases Members of the staff who were in direct contact with the patient have been confined within the hospital or if non-resident asked to remain within their own homes The remainder of the staff of the hospital will continue to work in the usual way and are not confined to the hospital All contacts of the suspected case will have been vaccinated during the week-end The clinical diagnosis of smallpox has been confirmed and a relative of the patient has been admitted to a smallpox hospital as a suspected case There is *no* indication for mass vaccination of the general public All those who might receive immediate benefit from vaccination are being visited "

Vaccination within the Borough

A sustained effort followed on Saturday afternoon and Sunday to secure the vaccination of all known contacts in their own homes For this purpose the deputy medical officer of health organised three parties comprising doctor, health visitor, and public-health inspector, to carry out house-to-house vaccination of all contacts Concurrently the deputy area medical officer and area chief clerk opened an emergency vaccination centre at Chestnuts, St Ann's Road, which was continuously staffed over the weekend and for as long as necessary thereafter

Hyperimmune Gamma-globulin

Since doubts were felt about the effectiveness of vaccination so late after contact with the primary case, it was decided to reinforce vaccination with anti-variola gamma-globulin Application was at once made to the Ministry of Health, and half the available stock was released This amount was divided equally between the hospital and public-health departments A dose of 10 ml (1000 mg) for an adult and 5 ml (500 mg) for a child was given to the previously unprotected primary contacts In practice it was found that much patience was needed in preparing the injection The protein proved extremely difficult to get into solution or suspension, and each dose took about ten to fifteen minutes to prepare

Origin of the Infection

In midsummer, in a patient with no known history of recent arrival from, or links with, those parts of the world in which smallpox is endemic, a report of smallpox must immediately arouse two considerations in the minds of those in the central government department concerned with smallpox—that there has been a misdiagnosis (for smallpox in this country is nearly always imported during our winter), or that if the diagnosis proves correct, the disease must have been present in the country, unsuspected, for some little time, and that evidence of this can be found if search is made in the right quarter

In the incident now related examination of case 5 had left no doubt as to the diagnosis No case of smallpox had been notified for some three years, and there had been no recent suspicion of the disease. It was quickly established that there was no link or association between cases 4 and 5 and any foreign country Few could have led a more circumscribed existence than the widowed grandmother, and the boy's (case 5) small world did not extend outside his part of the borough By inference, therefore, it seemed wellnigh certain that a study of recent and not-so-recent death certificates would provide a lead to the source of infection The complete absence of any reported cases of smallpox elsewhere in the country suggested either that the earlier missed case (or cases) must have been modified clinically and have arisen in a patient who was himself vaccinated and belonged to a small well-vaccinated group, or that in this earlier case the patient must have died before his disease had reached the infectious stage The search was therefore at once narrowed to a retrospective inquiry for someone who had died in the early stages of hæmorrhagic smallpox, and the presumption was that the cause of death most likely to have been assigned would be leukæmia Accordingly, at the suggestion of one of us (C G N) a scrutiny was made of all death returns for the past four months, and 4 deaths during that time seemed worthy of investigation, the stated cause of death in all cases including the term "leukæmia" Further inquiries readily disposed of any possible suspicion in the first 3 cases, late residents of Tottenham, but in the case of the fourth (case 3), a licensee lately of the adjoining borough of Islington, an interview with the widow revealed that she and her late husband had visited his brother (case 1) in Wembley, who, with his daughter (case 2, aged 8) had been suffering from "chickenpox" Thirteen days later case 3 became very ill and was admitted late at night to St Ann's General Hospital

This patient had had an acute febrile illness with hæmaturia, massive purpura, and an enlarged liver and spleen, from which he died four hours after admission The leucocyte-count was 28,000 per c mm, 48% of which were primitive cells of the polymorph series *Hæmophilus influenzæ* and pneumococci were recovered in large numbers from a blood-culture As the cause of death was uncertain, the coroner was notified and the body removed to the Prince of Wales's General Hospital for necropsy The purpuric condition, with a leukæmoid blood film, suggested a diagnosis of acute leukæmia, but in retrospect he must be regarded as a case of hæmorrhagic smallpox

Necropsy specimens were sent to the pathology laboratory, where it may be assumed that the cleaner (case 4) became infected The brother-in-law (case 1) of Wembley, a well-vaccinated subject, had returned to this country by air from Lagos, Nigeria, on March 29, and on April 11 had developed a mild illness diagnosed at the time as chickenpox His daughter (case 2), aged 8, vaccinated in infancy, became ill on April 25 also with a mild attack of "chickenpox", but was said to have had a previous attack of chickenpox In retrospect both father and daughter probably had smallpox, and were the source of infection of case 3

Progress of Outbreak in the Borough

Throughout Sunday, June 30, the immediate focus of attention was on the primary contacts Systematically the lists were worked through and gamma-globulin and vaccination, or revaccination alone, was given to the members of the public at greater risk—there were no refusals

A girl, aged 11, not a contact of case 5, was sent on suspicion to Long Reach Hospital, but later proved to have chickenpox An aunt of case 6, who had been vaccinated in infancy and had nursed case 4 (her mother), became unwell and the following day was admitted to Long Reach Hospital, smallpox was later confirmed In due course she made a slow but uneventful recovery The engineering firm where case 6 worked was visited and the staff were advised to accept vaccination Other primary contacts of special mention, living in the neighbourhood, included a married couple and their daughter, the wife of a U S A F airman, who was expecting her first baby at the time She was given gamma-globulin intramuscularly Later in the week she was admitted to an isolation cubicle at the American Hospital, Ruislip, for a normal delivery

The public-health inspectors meanwhile continued to obtain names and addresses of groups of persons at special risk (e g, laundry workers who might have handled contaminated linen from families involved), and directed them to the emergency vaccination centre Gradually the public at large pressed in ever-increasing numbers for vaccination These were diverted to their own general medical practitioners, who obtained supplies of calf lymph held at the Town Hall In the meantime vaccination of children at the school attended by case 5 proceeded well, and was undertaken by the mobile teams of doctors and health visitors The classroom of the patient, and the rooms at the houses where his and other cases of smallpox arose, had been sealed and disinfected Vaccination or revaccination of the ambulance workers at the Edmonton depot was arranged by the medical officer of health of Edmonton

On Tuesday and Wednesday, July 2 and 3, routine home visiting of primary contacts was continued, and many cases needed daily observation, including hospital out-residents and special cases referred by doctors in the district and health visitors—many of these were reactions to vaccination This surveillance continued for sixteen days

Notification of Chickenpox

Because of the close contact with local doctors, who agreed to report all cases of chickenpox, it seemed unnecessary in the early stages to seek action under Section 147 of the Public Health Act, 1936

General Liaison

Under the direction of the chief clerk, rapid compilation of records and distribution of information became the first task of the public-health officers

Other work was put aside except for matters of absolute urgency, and the whole staff concentrated on control of the outbreak This called for sustained work until late at night throughout the first weekend and following week Bulletins to general practitioners and adjoining medical officers of health were sent out daily Lists of contacts, which arrived from St Ann's Hospital and other sources, were classified according to the districts where they lived The medical officers of health of the districts concerned were first telephoned and the information was confirmed the same day by letter For those living within the borough, contact sheets were made out and passed to the district public-health inspectors who undertook surveillance for sixteen days

Besides the information which had to be telephoned out, there were continuous incoming telephone messages and inquiries As a result, despite six telephone extensions in the department there was often an acute shortage of telephone facilities It was also necessary to arrange for the switchboard operators to stay on duty to deal with calls which continued throughout the evenings

National Insurance Benefits

None of the smallpox patients was a contributor for National Insurance benefits, but some primary contacts were able to claim upon the certificate of the medical officer of health

A special emergency procedure, laid down in a Ministry of Pensions and National Insurance memorandum for dealing with claims arising from an outbreak of smallpox, relieves the local national insurance office of any direct contact with the claimants The effect of this was that the public-health department was called on to act as agent for all the claimants It was thus necessary to arrange for the contacts to complete various benefit-claim and authorisation forms, which were retained in the department, and from these to complete weekly certified summaries, which were forwarded to the Ministry of Pensions and National Insurance A lump sum covering the benefits accruing was paid weekly to an officer in the public-health department, who was responsible for its distribution to the claimants

Compensation for Loss of Earnings

Section 51 of the Tottenham Corporation Act, 1952, enabled the local authority to compensate primary contacts for loss of earnings resulting from their exclusion from work The Corporation agreed that compensation should be paid to the extent of making up the difference between the earnings lost and the national insurance benefits received Fortunately the early restriction of the outbreak so limited the number of primary contacts that expenditure on this account did not exceed £100

Supplies of Goods to Households in Isolation

A particular difficulty was that whole households had become primary contacts and were subjected to isolation within their homes This meant there was nobody available to do essential shopping, and in one or two cases the families had no ready money to pay for the goods needed A health visitor was, therefore, asked to visit these families daily and to do any necessary shopping on their behalf Recognition is due to the local tradesmen for their ready cooperation in providing goods on credit pending settlement of the families' claims for National Insurance benefit

Distribution of Calf Lymph

Lymph was made available to doctors at the Town Hall The demand grew rapidly after the first weekend, and altogether 11,500 units were obtained for use by family doctors and at the public vaccination centre 4291 units were issued to medical practitioners and the remainder used by the local authority staff A certain amount of wastage resulted from the use of lymph supplied in multiple units of 10, 25, and 50

Summary

An outbreak of smallpox in Tottenham in 1957 is described

The disease probably entered the country when a man incubating it returned from Lagos 6 probable or confirmed cases were traced, 4 patients, who had been vaccinated, survived, and 2, who had not been vaccinated, died

Anti-variola gamma-globulin was used to give additional protection to the previously unvaccinated primary contacts No secondary case arose within this group, and it seems that this may have in part been due to the protection afforded by the gamma-globulin

We wish to express our appreciation of the part played by all public-health and hospital staff, and particularly to thank Dr J Epsom and Dr J M Medlock

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No Smallpox in Lincolnshire

Our report last week of a confirmed case of smallpox at Scunthorpe was unfortunately incorrect A clinical diagnosis of smallpox was made in a 30-year-old Arab and he was admitted to Laceby Hospital Laboratory tests were negative, however, and further inquiries disclosed that the man had been in close contact with children suffering from chickenpox

Scotland in 1957

According to preliminary figures[1] in Scotland the birth-rate last year was 19 0 per 1000 population, compared with 18 5 per 1000 in 1956 The stillbirth-rate—24 per 1000 live and still births—was the same as in 1956 The death-rate was 11 9 per 1000, which is 0 1 below the rate for 1956 The maternal-mortality rate (as in 1956) was 0 5 per 1000 live and still births The infant-mortality rate (as in 1956) was 29 per 1000 live births, and the neonatal death-rate was 20 per 1000, which was 1 above the rate for 1956 The death-rate from tuberculosis (all forms) was 14 per 100,000—9 below the five-year average

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[1] Quarterly Return of the Registrar General, Scotland Births Deaths and Marriages registered in the quarter ended Dec 31, 1957, also preliminary return for the year 1957 H M Stationery Office 1958 Pp 40 2*s* 6*d*

Conferences

STRESS DISORDERS

A CONFERENCE organised by the Society for Psychosomatic Research was held in London on May 2–4.

Relation of Stress to Three Groups of Disorders

ESSENTIAL HYPERTENSION

Dr JOHN HAMBLING (Canterbury) described the correlation observed in the labile hypertensive between fluctuations of diastolic blood-pressure and discussion of emotionally charged topics. Suppressed rage and resentment were the most potent diastolic pressor factors. To verbalise or act out these feelings could produce a dramatic fall in pressure. The potential hypertensive usually had at least one parent who was dominating or driving, and he tended to see his life situation in terms of dominance-submission, being ultrasensitive to any authoritarian element.

ITCHING SKIN DISORDERS

Dr BRIAN RUSSELL outlined the neurophysiology and biochemistry of normal and pathological itching. It might ultimately be found that emotionally activated itching had a biochemical mechanism, but this was still unknown. Itching sensations were conveyed by the non-medullated C sensory nerve-fibres and were a form of weak protopathic pain. A stimulus of greater intensity eliminated the itching and replaced it by burning pain, often more tolerable. This itch→burning pain→itch sequence might explain the maintenance by scratching of some dermatoses. It was often difficult to establish the temporal link between "stress" and itching skin disorders without prolonged observation. Dr Russell drew attention to the psychological significance of the terms associated with itching and irritating skin conditions. In his experience itching skin disorders were more often associated with aggressive than with libidinous impulses. Pruritus might occur when a person feared to give expression to repressed or guilt-laden drives.

GASTROINTESTINAL DISORDERS

Dr DESMOND O'NEILL prefaced his remarks with the reminder that disease should be considered in terms of reaction patterns rather than of systems, a new taxonomy was needed, and what Dr Michael Balint called "the pathology of the whole person" had still to be written. The gastrointestinal system reacted to stress in many different ways. Overeating, leading to obesity, was the reaction of some patients to feelings of depression and discontent. Under-eating might alternate with this, or might progress to anorexia nervosa because of guilt about eating. Recurrent vomiting in children was another familiar reaction. In his experience duodenal ulcer was a stress disorder, gastric ulcer not always so. Another syndrome he called "abdominal discontent": the patient felt "fed-up," and complained of heartburn, flatulence, and discomfort, and had sexual difficulties. Most recurrent abdominal pain of which the cause was known could be related to stress. Diarrhœa, constipation, and ulcerative colitis were other disorders of the gut in which the relation to stress was well recognised.

Dr PHILIP HOPKINS said that, in his general practice, of 259 patients with stress disorder 45 had gastrointestinal symptoms. These had responded to simple psychotherapy with improvement, maintained over five years' observation.

Dr NICOLAS MALLESON said that of 500 university students to whom he had given a questionary 150 had reported some disorder of the gut. Stress disorder seemed to show itself more commonly in this system than in any other. He thought this might be because the human stomach, as was suitable to a ground ape, secreted gastric juices all day long. We were built for a casual omnivorous diet, but in modern life we ate like carnivores—alternately gorging and fasting.

Experimental Stress

STRESS IN AVIATION

Group-Captain V. H TOMPKINS (Portsmouth) said that the effect of stress on the airman had been the subject of discussion since the earliest days of flying. As Dr Denis Williams had pointed out, the stresses to which the nervous system of the airman had to become adapted were threefold: the way of life, the job, and the physical conditions of the job (speed, radial acceleration, oxygenation, cold, &c.). It had been found in practice that in these physical conditions there was no specific stress factor comparable in its effects to the psychological factor of fear. Fear was considered responsible in 99.6% of a series of 2200 flying crew who broke down with neuroses. Somatic reactive stress symptoms were usually mild or transient in airmen, who were highly selected. He had the impression that men with mild obsessional traits were more apt to show such symptoms.

EXPERIMENTAL STRESS IN MAN

Dr D RUSSELL DAVIS (Cambridge) discussed the problems encountered by the psychologist attempting to study this subject. Pavlov's dogs, posed an insoluble problem, would develop "experimental neurosis", but the man had a wider range of solutions, his interest was less easily engaged, and he readily "withdrew." Methods using non-specific stimuli such as electric shocks or loud noises yielded little of importance. He had overcome these difficulties in some war-time studies, subjecting pilots to tests of their newly acquired skills. He paid tribute to the work of Kurt Lewin and Zeigarnik. Laboratory methods, however, remained unsatisfactory for the study of sustained stress: its effects were better observed in natural experiments and by clinical methods.

ANIMAL OBSERVATION

Dr R A HINDE (Cambridge) spoke of some studies of the behaviour of animals in nature under stress. Short-term autonomic responses to stress—for example, when two conflicting tendencies were present—might result in a compromise form of behaviour or in a "displacement activity." Many "displacement activities" were now thought to depend on autonomic response to one or other conflicting tendency. He also discussed the theories about the population cycles of certain wild animals, and why after a peak period the population may fall rapidly or "crash". Some workers had described a syndrome marked by liver atrophy and hypoglycæmia in animals that died during the crash period. Selye had pointed out that this "shock disease" resembled a disease of adaptation. This agreed with the finding of a direct relation between adrenal weight and population density in mice in the laboratory.

PHYSIOLOGY OF STRESS RESPONSES

Dr W J H BUTTERFIELD presented the results of his studies of volunteers receiving oral hydrocortisone and of 25 burned patients. Most of the metabolic changes caused by burns could be mimicked by hydrocortisone The size of the metabolic response was roughly proportional to the stress, measured by the percentage of the body burned The liver's failure to metabolise adrenal steroids might play an important role in metabolic changes after burning A further effect of this was the development in some burned patients of diabetes of Cushing-disease type, this might later become insulin-dependent

Stress and Occupation

STRESS DISORDER IN SOCIETY

Dr F M **MARTIN** (Edinburgh) said that epidemiology, had so far contributed little to the study of stress disorder This was because the two prerequisites of accurate counting and significant analysis of data were so rarely fulfilled There was need for the sociological as well as the clinical approach in gathering and evaluating data When rapid changes were in progress in a community the sociologist would focus attention on the stresses this might cause In more stable societies he would look for dysfunctions in the organisation of society and the effect on the individual of his quest for culturally sanctioned goals There was a danger of circular reasoning He did not think the concept of " the stress and strain of Western civilisation " very helpful Hypertension fitted in with this, but duodenal ulcer was common not only in the American Negro but in natives of Nigeria and of South India He thought that the factor of social cohesion merited attention, this had been shown to be significant in the epidemiology of suicide and schizophrenia In this way the social scientist could hope to throw light on stress disorder

STRESS IN INDUSTRY

Dr J J **O'DWYER** felt that industry and work conditions were often blamed for stress caused by family or social maladjustments The social contacts in industry were important, and promotion often caused stress because it made even a charge-hand feel somewhat isolated In managerial staff it might involve the individual and his family being uprooted to move to where the higher job was The industrial medical officer and the general practitioner each knew too little of the other's view of the worker-patient

THE UNIVERSITY STUDENT

Dr **MALLESON** said that about 70% of the students of University College, London, consulted the physicians of the student health service during their three-year course of studies They usually came with some physical symptom, mostly as a face-saving excuse for seeing the doctor for troubles which they themselves attributed to " nerves " The stress affecting the average student fell into two main categories adolescence (sex problems, leaving home, self-management, " growing-up ", &c), and studying for a degree Figures for 1950 and 1951 showed that the more severely neurotic student failed his examinations about twice as commonly as the average, but the slightly neurotic had a lower-than-average rate of failure For the student, as for civilised man, it might be a choice between stress and stagnation

The Person in his Family Setting

THE FAMILY DOCTOR

Dr H N **LEVITT** said that, as a general practitioner, he would agree with Dr Stephen Taylor's estimate that at least a third of general-practice cases were psychiatric The bulk of dyspepsia he himself saw was non-organic The family doctor could often see the effects of the pressure of family, home, neighbours, work, and community, like concentric rings in a magnetic field, surrounding and influencing the patient Sometimes, to break the circuit, removal of the patient to hospital or nursing-home was essential

PERSONALITY DEVELOPMENT

Dr **JOSEPH SANDLER** described the case of a married woman, aged 35, treated by psychoanalysis for vaginismus and phobic symptoms It had become clear in the analysis that the patient had unconsciously sought a stressful condition as a means of gratifying masochistic needs and of averting worse evils

STRESS IN CHILDHOOD

Dr **JAMES ANTHONY** said that in considering stress disorders in children it was difficult to distinguish correlation from causality In one series of 100 children with bowel-training difficulties there was found to be strong correlation between the type of training and later behaviour Strictness and insistence on early sphincter control by the mother was found to result in the child's encopresis or strong aversion to fæces, and undue laxity in training to be connected with soiling Sleep disorders were also associated with stress The child with eidetic imagery was more likely to have nightmares, while the child of haptic, kinæsthetic make-up reacted by sleep-walking

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Special Articles

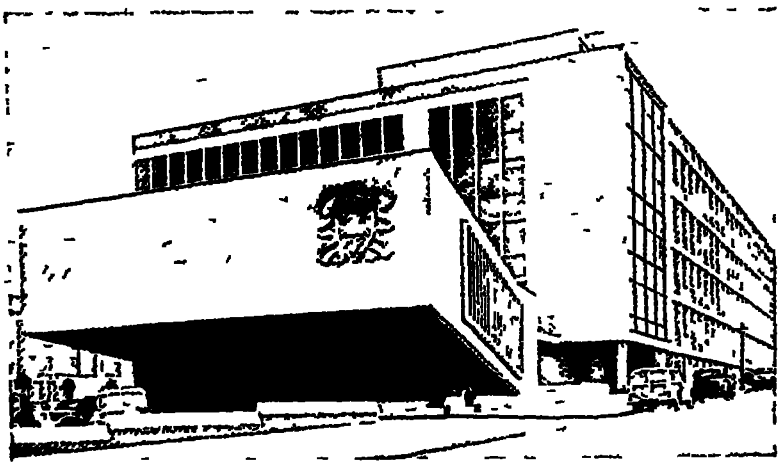
THE NEW LIVERPOOL MEDICAL SCHOOL

THE growth of all departments and the creation of new ones has meant that the medical school at Liverpool (like many others) has been spread around the precincts of university and hospital—in a converted house, a former nurses' home, and part of the city laboratories At last many departments—of pathology, bacteriology, medicine, pharmacology, and obstetrics and gynæcology, with the subdepartment of radiodiagnosis—have been gathered into a new building in Ashton Street

The department of medicine has well-equipped laboratories (provided through the generosity of the family of the late Sir Montague Burton) where electroencephalography and hereditary factors in disease are among the subjects investigated In the department of pharmacology and general therapeutics the studies include the action of drugs on the nervous system, myasthenia gravis, and the thymus In the department of pathology, formerly housed in the Thompson-Yates Laboratories opened by Lord Lister sixty years ago, work is in progress on endocrine aspects of cancer, and in the department of obstetrics and gynæcology cancer in women, toxæmia, and sterility are being studied The work in the department of bacteriology includes investigations on the viruses of smallpox and poliomyelitis and on tissue cultures Each department is housed on one floor, except that the department of pathology occupies most of two floors

Besides these departments the new building contains three lecture theatres and class laboratories for the 506 undergraduate and 177 postgraduate students, as well as the dean's offices, a staff common-room, and a committee-room

Designed by Mr A G Bullen, F R I B A, the building has a flexible plan, for the floor-space on each storey is unbroken, rooms of any size can be made by internal partitions based on mullions at five-foot intervals along the perimeter The frame is of reinforced concrete, with prestressed concrete beams The facing is also of concrete, except for Portland stone on the Pembroke Place elevation (illustrated here), where the principal lecture theatre projects from the main building in a striking manner The whole building is centrally heated and air-conditioned, with provision for removing noxious gases (e g, formaldehyde) and preventing the spread of infection It is hoped to link the present building with a further block fronting Elizabeth Street the completed medical school will then house all departments of the faculty



The new building was officially opened on Wednesday, May 7, by H M Queen Elizabeth the Queen Mother, after an address by Lord Cohen of Birkenhead, professor of medicine in the university, who sketched the development of the Liverpool School of Medicine from its foundation in 1834 He said that the pride of a school "lies not simply in the beauty and dignity of its architecture, but in the contribution which those who labour within its walls make to 'the advancement of learning and the ennoblement of life'" He referred to the work of three great Liverpool contemporaries—Sir Ronald Ross, Sir Robert Jones, and Sir Charles Sherrington, all born a hundred years ago

Later, at a congregation in the Philharmonic Hall, the honorary degree of LL D was conferred on Her Majesty, and on Lord Adrian, Sir David Campbell, Sir Allen Daley, and Sir John Hobhouse Speaking on their behalf, Her Majesty paid tribute to the part Liverpool had played in advancing medicine, in Liverpool, she said, "visitors are conscious of a pulse like a hammer and a vigour which nothing can daunt"

Parliament

An Institute of Criminology

ON the adjournment on May 7 Mr MONTGOMERY HYDE pointed out that, unlike other European countries and the United States, we had in this country no institute of criminology though it was generally agreed that crime and its methods of prevention and treatment deserved careful and detailed study No university in the United Kingdom had a chair of criminology, though Cambridge had a department of criminal science with a director at its head Otherwise the university teaching of criminology in this country usually formed part of the syllabus for the study of sociology, psychology, or other social sciences At present, readerships in criminology existed only in Oxford and London, the latter tenable at the London School of Economics and Political Science Some of the provincial universities provided courses in the subject or some branch of it, but teaching was mostly confined to a few odd lectures, though at the Queen's University, Belfast, special attention was paid in the department of psychology to juvenile delinquency No degrees or diplomas in criminology were available here A British institute of criminology could coordinate the teaching and research If it were to concentrate at first on postgraduate work, its activities might stimulate the teaching of criminology to a graduate level in the universities Then, if it set the high standards which were to be expected, a qualification in criminology might well become desirable or even obligatory for those concerned with the administration of justice Later non-diploma courses conducted by the institute for justices, police, probation, and prison officers could prove of value, not least as a common meeting ground for discussion

Sir GEORGE BENSON paid tribute to the work of the new Home Office research section But its research was intensive and practical, and it was no substitute for an institute which would be a general educational force in the community We allowed our courts, our magistrates, and the whole administration of the penal system of the country to rest on pure guesswork and tradition Nowhere at present could the court and the penal machine look for guidance and information An institute of criminology was a vital need

Mr DAVID RENTON, the joint Under-Secretary of State for the Home Department, said that the Home Secretary had been giving much attention to the suggestion made to him by the Howard League that the time had come to encourage the establishment of an institute of criminology in this country He was convinced that the vigorous pursuit of research into the causes of crime and the treatment of offenders was urgent especially at a time when crime was increasing and none could say what were the fundamental causes of that increase Mr Renton himself thought that such an institute would have two ends—to train, preferably at postgraduate level, those who would carry out research and teach others in future, and to provide teaching facilities for those who were concerned in their daily work or in voluntary service with the prevention of crime, the administration of justice, or the treatment of offenders—for example, magistrates, probation officers, members of the police force and of the prison service In addition, such teaching might help to form a better-instructed public opinion

Much had been done in recent years to increase research and develop teaching in this field, and the Home Office had done its best to give such help and encouragement as its resources would allow Research was being planned or was being carried out on the nature of group relations in prisons, the changes brought about as a result of the "Norwich" experiment, the sentencing practice of the courts, the social consequences to offenders of being convicted and sentenced, crimes of violence in the Metropolis, and the development of prediction studies He agreed that Great Britain was today almost alone in having no institute for the study and teaching of criminology, no chair in criminology at any university, and no separate university qualification in this subject It might well be that a stage had been reached where the establishment of such an institute within one of our universities would be of great value, in order to give a new impulse to studies in this field, to set high standards in a subject whose academic status had not yet been fully recognised, and also to meet a growing demand for teaching in this subject The Home Secretary accepted that view and he had undertaken informal consultations with university authorities Those consultations were still in progress, and were necessarily still confidential, but he hoped that they would lead to useful results

Professional Income-tax Allowances

In moving the second reading of the Finance Bill on May 12 Mr J E S Simon, financial secretary to the Treasury, said that clause 14 embodied a proposal which would receive much support Relief would be allowed for annual subscriptions to professional and learned societies with activities related to the employee's work Subscriptions to Associations such as the medical defence Associations and the statutory registration fees, set out in the fifth schedule, paid by such people as architects and dentists as a condition of being allowed to practise, would also be allowed The Commissioners of Inland Revenue would approve societies for the purpose of allowance of subscriptions by reference to the criteria which were laid down in the body of the clause, and subject, of course, to the usual rights of appeal The general test would be whether a society's activities were wholly or mainly of a professional or learned character Where such a body also had significant activities of a different kind, such as the prosecution of salary claims, the clause provided for the deduction of a fairly apportioned part of the subscription

Mr Eric Fletcher here asked whether it was intended to deal with subscriptions paid to learned societies by way of covenant? Until recently these had the advantage of enabling learned societies to recover the tax paid A recent decision in the Court of Appeal had brought about a different result Was clause 14 intended to restore the position in that respect? Mr Simon replied that clause 14 did not deal specifically with that matter, although, where the institution otherwise qualified, money paid under the covenant would rank as a deduction

QUESTION TIME

Poliomyelitis Vaccine

Mrs Barbara Castle asked the Minister of Health what target he had set for the production of anti-poliomyelitis vaccine by Messrs Glaxo and Burroughs Wellcome, respectively —Mr. Derek Walker-Smith replied It continues to be the Government's intention that, as soon as supplies are sufficient, only the British type of vaccine should be used in the vaccination scheme The manufacturers are aware of this, and the issue of individual invitations to produce vaccine does not arise Nor is there any question of the Government setting a production target for individual firms

Mr Cledwyn Hughes Is the Minister aware that in many cases the British vaccine is being given for the first vaccination and a foreign vaccine for the second? Would he say whether that is approved by his Ministry's experts?—Mr Walker-Smith It is quite all right, on medical grounds, to vary the type of vaccine between the two injections

Mr Richard Fort asked the Minister when the substantial new supplies of Salk vaccine would become available for use in this country —Mr Walker-Smith replied 2 million doses of Salk vaccine which have passed their tests and been licensed for issue in America are due to arrive on May 13, and they will be distributed immediately to local health authorities Another $1^1/_2$ million doses of this vaccine are expected next week In addition, a batch of $^1/_2$ million doses of British-tested Salk vaccine is now being distributed, and further supplies are expected as tests are completed

London Teaching Hospitals

Mr Marcus Lipton asked the Minister what plans he was now considering to reduce or change the number of London teaching hospitals —Mr Walker-Smith replied None, Sir

Mr Lipton Has the Minister seen the reports stating that he is considering closing three London hospitals—Charing Cross, St George's, and Westminster? Is there any truth at all in those reports?—Mr Walker-Smith I did see a report in a usually well-informed newspaper, but, in fact, I am not considering that course There are certain proposals in mind with reference to Charing Cross and the Royal Free Hospital, but there is no question of amalgamation

In England Now

A Running Commentary by Peripatetic Correspondents

Reactions to the bus strike make an interesting medico-social study Observations outside a large South London hospital showed that over the first four days the passenger/car ratio increased from 1 7 to 3 2, a difference held to be significant at the 1% level and the increase appearing to be linear against the log time Unless the curve starts to flatten out there will be people sitting on the roof At busy times the cars queue up at bus stops waiting to offer lifts Further effects are less easy to measure directly, but one may readily conjecture a few the increasing networks of little friendships for a start " Oh do you always come this way, that *would* be kind ", then " Tomorrow morning as usual then ", and finally " Do bring the family round this Sunday " The increase of togetherness and raising of morale, not to mention chance romantic encounters, cannot but have a good effect on the mental welfare of the community as a whole, and hospital admissions should soon reflect this if Messrs Macleod and Cousins can be persuaded to remain adamant

Apart from the weather, we haven't had a direct stirring challenge for a long time and it will do us good My wife's evening class, for example, was on the first night of the strike and is never very well attended I said surely no-one would turn up, so she might as well get on with the supper, but it didn't work I had to drive her there and there was the biggest turnout of the year Motivational research should get going here did the class overcompensate to the difficulty as one man, or rather one woman? Or were they bored after a long day at home? Or was there some contaminating factor? A fruitful field awaits the enterprising worker these situations must be exploited by those pursuing PH D s

The effect on the busmen may be less happy, though in course of time the differential between drivers and conductors of peptic ulcer and coronary thrombosis (Morris 195-something) should iron out A survey of how strikers spend their time would be worth while Do conductors wander nostalgically up and down stairs? A number of them, of course, have their duties to attend, and face the same difficulties of getting to work as the rest of us A friend of mine offered a lift to a stranded bloke yesterday and only at the end of 15 miles did he discover his passenger was a strike picket going to his station

There are other smaller groups to be considered of course A friend in the bicycle and scooter trade is in danger of passing into an acute hypomanic state give the strike another fortnight, he says, and he will retire Trade-union officials, one fears, may be liable to anxiety attacks, and then of course there's the Government Apart from fluctuations in blood-pressure we would rather not commit ourselves on this delicate subject perhaps a medical M P could be persuaded to fill this gap in our scientific knowledge

* * *

It has been a good lambing time and the countryside is full of the attractive youngsters, playful, thoughtless, and impulsive, just like our own children I met three ewes and their lambs yesterday as I entered the enclosed road when coming off the fell from seeing Charlie's children The ewe on the offside had her lamb with her, so I steered quietly between the mothers, but one of the lambs on the nearside evidently belonged to her, and at the very last moment he dashed across the road and disappeared from my view behind my nearside wing Sixpennyworth of rubber left my tyres in a cloud of smoke, and I didn't feel a wheel go over him, nor did I feel him hit me, but I got out with a very empty epigastrium, and there, in the road behind, he lay, very still and with his nose bleeding I carried him to the roadside, and after ten minutes or so he was holding up his head, looking for his mother and seeming much better So I left him and went back to lunch, intending to go up and see if he was all right after afternoon surgery

Charlie came down for the children's medicine before I left, so I asked him if he had seen the lamb "Yes," he said, he had seen it It had a dirty nose and he thought it had had an accident, but it was with its mother and quite all right, and I was not to worry about it My wife heard this bit of conversation, and after he had gone she gave me one of those quizzical motherly smiles that she keeps for me when she finds out something that I hope she won't notice "So that was what was the matter at lunchtime," she said "You hardly ate a thing and didn't say a word If a lamb does that to you I hope to goodness you never run over a child" Remembering the empty epigastrium as I got out of the car, I hope to goodness I never do

* * *

I know a hospital where the Royal Arms, in all their splendour of gilt and scarlet, are floodlit above the portico and where an alcove in the entrance hall is occupied by a portrait of a beautiful Queen Consort The corridors are decorated in contemporary colour schemes and adorned with boxes of growing flowers and tanks of tiny coloured fish The wards are divided into four-bed and two-bed cubicles, also in contrasting colours, and with sound-proof ceilings, and the ward kitchens are equipped with stainless steel sinks and cupboards The surgeon's clients are anæsthetised to the sound of music under a painted ceiling Can this be the National Health Service? Of course not It is a well-known military hospital not far from Lambeth Bridge

* * *

The ordering system in our department is complex, with numerous highly coloured forms to be signed in triplicate Just recently it became our duty to sign them, and we were fascinated to find what the department had been running on all these years We even got round to making tentative little inquiries of our formidable senior technician when we found him in a good mood "What," we would ask timidly, "do we *do* with all these assorted grummets?"

After a time we became a little bolder and actually attempted to strike out one or two items, but it made no difference, they always came back on the next order form, and we were given to understand that interference of this sort made the department almost impossible to run Eventually we became almost anæsthetic, and nowadays we sign our name without a moment's thought to "36 only alum pudd steamers, complete with lid"

But the other day our eye was caught by an item reading

1 only tin tray with picture 4s 0d'

We no longer dare to approach our senior technician on matters of this kind, but we sent at once for our new secretary, who is always glad to enlighten us It seems that the Professor's tea tray had become a Disgrace, that a tin tray with a picture on it is cheaper than a tin tray without one, and that the picture would almost certainly prove to be a spaniel, the trade considering spaniels to have maximum sales appeal

Convinced by these telling arguments, we signed without demur, and it was not until the matter came up at the afternoon tea club yesterday that we remembered that the Professor is greatly attached to his fox-terrier A rough canvass of departmental opinion only too clearly supported our fear that the appearance of a spaniel might be regarded as a studied insult It was widely felt that we had been too precipitate, and should have specified a psychologically neutral picture We were forced to speak sharply to one of our demonstrators, and our senior lecturer, who owns a Siamese cat, referred slightingly to dogs in general At this a visiting dog-lover from biochemistry swallowed a cigarette in his agitation, and had to be revived with copious draughts of hot water The meeting broke up in a general huff, and our migraine came on worse than ever

It was therefore with some relief that we welcomed this morning an end to the suspense in the shape of the arrival of the tray itself "We have pleasure," said the accompanying letter suavely, "in supplying to your specification 1 only tin tray with picture, price 4s 0d, and trust that it will meet your requirements adequately"

With trembling fingers we undid the string It was, of course, *The Boyhood of Raleigh*

Letters to the Editor

TOXOID OR A T S?

SIR,—It is perhaps not generally realised that considerable sections of the civil population have received and are receiving active immunisation against tetanus These sections include (*a*) those young men who have completed their National Service, (*b*) the increasing number of young children who are immunised with triple antigen, and (*c*) an appreciable number of older children from independent schools where routine active immunisation is practised

In the event of injury these individuals should be given a booster dose of tetanus toxoid It is unnecessary and indeed undesirable to run the risk of sensitising them to horse serum by administering A T S Members of my Association do their best to instruct actively immunised individuals that they should ask for toxoid in place of A T S if they are the victims of an accident Nevertheless it has been found that this request is all too frequently disregarded particularly in busy casualty departments and A T S is given willy-nilly

I have been instructed by my Council to bring this point to the attention of the profession through your columns We would wish that all individuals who are actively immunised should be clearly instructed that they have received *toxoid* and are to ask for this to be repeated if they sustain an injury On the other hand, we invite casualty officers and others to bear in mind the increasing possibility that the patient has been actively immunised, to ask in every case of injury if this is so and if the answer is in the affirmative to administer toxoid rather than A T S

THOMAS L SCOTT

Horsham, Sussex

Honorary Secretary, Medical Officers of Schools Association

SYMPTOMS AFTER CHOLECYSTECTOMY

SIR,—As a physician seeing many patients with gallstones, one must agree with Mr Burnett and Mr Shields (May 3) that the use of the term "postcholecystectomy syndrome" is not justified At the same time general physicians themselves see many patients who have had a diseased gallbladder removed without losing many of their symptoms In point of fact the results of this operation are not conspicuously good as far as my general experience goes Despite this it is certainly very proper to recommend removal of gallstones in nearly every case, but the reason for such advice must rest on certain general principles which are not covered by Mr Burnett and Mr Shields The benefits to the patients are long-term not immediate

Gallstones and diseased gallbladders must be removed for three reasons (*a*) to prevent further gallstone colic, (*b*) to forestall a nasty attack of acute cholecystitis, and (*c*) to prevent the remote danger of carcinoma of the gallbladder In these three respects I often feel that the operation is done as much for the benefit of the patient's doctor as for the patients themselves It is as well to point this out to the patient preoperatively so that they are not misled into thinking that passage through the surgical ward and loss of the gallbladder is going to restore them to complete mental and physical health

Exactly what symptoms a diseased gallbladder gives rise to is a matter which very few people can accurately define But when one remembers that in most instances the organ which is removed is not functioning and has failed to function for many years, it becomes quite clear that its simple removal cannot restore function, so the symptoms must continue Gallbladder function is not essential to digestion, but its absence will often be felt after greasy meals

This no doubt is the answer to the problem of the many patients who continue to complain after operation Even though the common bile-duct does distend it cannot take over the concentrating function of the gallbladder or produce a cistern-like flush of concentrated bile at the psychological point in digestion Whether this lack of concentrated bile does in fact give rise to symptoms of diseased gallbladder must be a matter for discussion, but it is certainly present both before and after operation and operation itself does nothing to alter this fact

But beyond this is the very frequent problem of whether what the patient complains of is indeed due to a diseased gallbladder Mr Burnett and Mr Shields have indeed pointed out that it is not unusual to find that postcholecystectomy symptoms have in fact been due to duodenal ulcer or some other intra-abdominal disease But more commonly the symptoms are due to a small hiatus hernia which has not been diagnosed or to simple reflux œsophagitis which has also not been suspected Because of these two conditions, it is my general practice to slim the patients before sending them to have their gallbladder removed, provided of course the patient is not suffering from repeated attacks of gallstone colic This simple process so often removes symptoms previously regarded as due to the gallbladder that unfortunately the patients are often reluctant to have their gallbladders removed

One further explanation of the poor result of cholecystectomy remains—namely, in most cases the sufferers are obese women in late middle life who are often suffering from hypertension, coronary disease, bronchitis, or some other organic disability which continues to give trouble after operation If the organic side is not at fault in these patients, they are emotionally battered and beset by large families, small incomes, and much work They would in any case give rather poor results after any form of surgery

We are at the moment going through a changing pattern in regard to cholecystitis which may make for better results in the future A diagnosis is now being made after the first or second pregnancy and gallstones or gallbladders are being removed in younger women with much better long-term results Operation at an earlier stage in gallbladder disease would therefore give better results and should be our aim But in summary the relatively poor symptomatic result after operation here is due to the fact that most of the symptoms complained of subsequently were really present before the operation was undertaken and could not be expected to be helped by surgery in any case

Liverpool **ROBERT KEMP**

SIR,—I should like to comment on the article by Mr Burnett and Dr Shields

In the summary and in the text they say that they found no evidence of biliary dyskinesia If their case-summaries are complete, I submit that the surgeons who operated on these patients did not look for a dyskinesia The only methods of diagnosing biliary dyskinesia accurately are serial cholecystography,[1] one of the methods of manometry,[2] and chronovolumetric estimation of bile,[3] which can be misleading One can, however, suspect a dyskinesia from the clinical history

All the cases quoted in table II, with the possible exception of cases 13 and 20, could well have a dyskinesia On the necessarily meagre details given in the tables I postulate that cases 7, 8, and 17, in addition to their vesical calculi, had a biliary vesicular stasis, probably due to a biliary hypotonia, which was neither diagnosed nor treated at the first operation The biliary hypotonia was the primary and more important abnormality and the stones the secondary The primary abnormality remained and so did the symptoms Case 10 almost certainly has a hypotonic dyskinesia The patients with duodenal ulcers may have had a hypertonic dyskinesia secondary to the ulcers at the first operation and may have it still

Mr Burnett and Dr Shields say, "We had intended to study patients with 'biliary dyskinesia', but we were unable to find one We conclude that this condition does not arise where cholecystectomy is done for such reasons as in this series" This conclusion, I humbly beg to suggest, is totally unwarranted if the authors took no steps to discover the presence or absence of dyskinesia, and they do not say that they took such steps as are necessary to make this diagnosis The information they give leads me to believe that had the necessary steps been taken a dyskinesia would have been demonstrated in the majority of their cases

Newcastle upon Tyne **J DUDFIELD ROSE**

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[1] Rose J D *Brit med J* 1959 i 360

[2] Mallet-Guy P Rose J D *Brit J Surg* 1956 44 55

[3] Varela Lopez J Varela Fuentes, B , Martinez Prado G *Arch Mal app digest* 1950 39, 797

USE AND TOXICITY OF SULPHONAMIDES

SIR,—In his letter of April 26, Dr Laurance asked for suggestions from the manufacturers as to a method for ending the confusion caused by the similarity of the names of 'Sulphamezathine' and sulphamerazine This is a situation which has also been causing us some concern, and with the idea of effecting an improvement we recently registered the alternative trade mark 'S-mez' for 'Sulphamezathine' Already we find it welcomed by doctors as distinctive and easier to write Further, and in line with Dr Laurance's final point, we have taken steps to ensure that the official *B P* name, sulphadimidine, is given prominence on all labels and literature for 'Sulphamezathine' and its preparations

Imperial Chemical Industries, Ltd ,
Pharmaceuticals Division,
Wilmslow, Cheshire

B C BRYANT

SEPARATION OF MOTHER AND CHILD

SIR,—In their letters commenting on mine of March 1, Dr Kräupl Taylor (March 22) and Dr Howells (March 29) raise rather different points Dr Taylor draws attention to certain shortcomings in a recent publication[1] and asks for further particulars these I shall try to provide on my return to England

Our discarding of certain data as unreliable was done on the basis of defined criteria and only when two independent judges were in agreement that one of the criteria had been met (see p 222) In our view it is the quality of the data rather than our handling of them which is most open to criticism My theoretical and practical conclusions naturally rest on a broader basis than these data alone

At many points Dr Howells and I are in agreement The distinction between separation and deprivation is discussed in the opening paragraphs of *Maternal Care and Mental Health*, while much of the second part is concerned with how best to care for children out of their own homes so as to avoid their suffering privation Further, we agree that much mental ill health in children arises from privation suffered by them while living in their own homes Where we seem to differ is in the weight we give to the emotional attachment that commonly exists between a child and his mother (and the rest of the family) and the anxiety and grief which result from the rupture of such relations He seems to suggest that separation without privation is of no consequence Admittedly, as Dr Howells' own work confirms, stays with relatives and friends whom the child already knows and trusts need have no ill effects The acute distress and anxiety which young children experience when placed with strangers, no matter how kind, is well attested however (e g, Heinicke [2]), while the records of children who have been moved from one good foster mother to another show that cumulatively such experiences can have very adverse results

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[1] Bowlby, J , et al *Brit J med Psych* 1956 29, 211

It is because the removal of a young child from his home to the care of strangers is usually productive of intense anxiety, misery, and anger (often even when the home he leaves is a bad one), and also because it all too frequently leads to further moves, that I believe it should be undertaken with great circumspection Efforts to improve the home, though requiring time, skill, and patience, are in many cases preferable in the long run.

As from Tavistock Clinic,
London

JOHN BOWLBY

IODINE PROPHYLAXIS OF GOITRE

SIR,—In a leading article in your issue of April 12, you advocated the addition of some form of iodine to all the table or kitchen salt sold in the United Kingdom, except that which might be demanded free from such addition "The United States, Switzerland, and New Zealand have been using prophylactic iodine for several decades, and goitre has notably declined in all three countries" May I point out that the iodinisation of salt is not required in the United States and that its general use there, or elsewhere, is scarcely a matter of "several decades" but of only two or three

Of greater significance is the fact that goitre has been diminishing in prevalence and intensity in Switzerland for more than fifty years before iodised salt was introduced into *any* canton.

In opening the First International Goitre Conference, the president stated "les goîtres enormes, difformes, qui frappaient autrefois l'observateur a premiere vue ont presque disparu" [3] He also called attention to the change in the proportion of recruits rejected from military service because of goitre from 10% in 1885 to 2·97% in 1912 and 1·3% in 1924–5 The figures later collected by Schaub [4] showed that the decrease was greater between 1905 and 1910 than in any similar period after the introduction of iodised salt

Similar changes have been reported from England [5 6] and many other places from Rumania to the United States, West Africa, and South America [7–15] In at least one instance, the disorder returned after an absence of about fifty years, to be regarded as a new disease [16]

In 1927, Cornwall and the Isle of Wight were among the districts in which were found the highest proportion of enlarged thyroids among schoolchildren Can it be seriously contended that their diets were more likely to be deficient in iodine than were those of the children of Bedford and Hertford with less than half the proportion of goitres or of Cambridge and Huntingdon with less than a tenth? [17]

The use of iodised salt is not without its possible dangers Many have not observed any ill effects but others have The literature abounds in instances, but I shall quote only from *advocates* of the use of iodised salt

In New Zealand, the number of patients admitted to public hospitals because of exophthalmic goitre during the five years following the introduction of salt containing 1 part of potassium iodide per 20,000, after a longer period with a lower concentration, increased by 7% although the number of those admitted because of other thyroid diseases fell [18]

In Lausanne, the proportion of adenomas of the thyroid encountered in *all* the necropsies increased from 1936–37 to 1946, in all except the lower age-groups, whether the comparison was between either or both sexes at the same age or between groups dying in 1936–37 with similar groups ten years older in 1946 [19] Marine [20] recognised that the introduction of iodised salt had been followed by an increase in the number of cases of hyperthyroidism He regarded this as a temporary phase, to disappear as the number of new goitres falls Perhaps his faith will be justified, but there is no good evidence that this will be the case or, if it should occur, that the use of iodised salt should be considered responsible

It may well be that the change from simple goitre to hyperthyroidism is not due to iodised salt but to unknown factors However, if one may argue *Post hoc, ergo propter hoc* to show that iodised salt has diminished the number of simple goitres, one may suggest that the same may hold for the increase in hyperthyroidism

Would it not be well to make another survey to find out if there has not been in England a great diminution in the prevalence of simple goitre since 1927? Or shall the United Kingdom join other nations in emptying the ocean with a pail when the tide is running out.

New York University College
of Medicine.

ISIDOR GREENWALD

REGIONAL DISTRIBUTION OF CONSULTANTS

SIR,—The figures for consultants, beds, and population for each regional hospital board (given in your issue of April 26, p 907) make interesting reading I calculated the number of beds and population per consultant and also the number of hospital beds per 1000 population in each region as follows (I have omitted the two smallest regions)

Region	*Beds per consultant*	*Population per consultant*	*Beds per 1000 population*
Newcastle	46	8867	5·2
Leeds	76	13,215	5·7
Sheffield	70	14,842	4·6
N W Metropolitan	42	9386	4·5
N E. Metropolitan	60	9789	6·1
S E. Metropolitan	56	9096	6·1
S W Metropolitan	50	9328	5·3
South Western	64	10,750	5·9
Welsh	68	11,102	5·9
Birmingham	57	11,390	5·0
Manchester	73	13,563	5·4
Liverpool	72	10,862	6·6

The variation is quite staggering, and if the consultant cover for the whole country were brought up to that of the best-staffed regions, I estimate about 1600 new consultants would be needed

Such "backward" areas as Leeds, Sheffield, Manchester, and Liverpool, in particular, need strong reinforcements, and Sheffield in addition is obviously short of beds It would be interesting to know the number of S.H.M.O.s in each region, and if these are known, perhaps you, Sir, would publish them It may well be that the regions poor in consultant cover are using an excess of S.H.M.O.s and, if so, this fact should be considered by the committee reviewing those S.H.M.O.s who claim to be doing consultant work. I rather suspect, however, that the areas with low consultant cover will also be low in numbers of S H M O s

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[2] Heinicke, C. M. *Hum Rel* 1956, 9 105
[3] Carrière, H. Comptes-rendus de la conference internationale du goitre Berne 1927 p xix
[4] Schaub F A Ueber Erfolge der Kropfprophylaxe. Dissertation Zurich 1949
[5] Webb W *Brit med J* 1886 i 686
[6] Turton P *Lancet* 1927, ii 1170
[7] Hirsch, A. Handbook of Geographical and Historical Pathology, vol 2 London 1885
[8] Osler W *Amer med Sci* 1893 106 506
[9] Republica Argentina Second and Third Census 1895 1914
[10] Campeanu, L Problema gusei cretinismului in Romania. Cluj 1924 French resume p 162
[11] Bérard L, Dunet C Comptes rendus de la conference internationale du goitre pp 276–302 Berne 1927
[12] Flamberti A M *Rass Stud psich* 1934 23 866
[13] Ortiz de Landazuri F et al *Rev Clin españ* 1949 38, 304
[14] Greenwald I *J clin Endocrin* 1950 10 1309
[15] Kreuger E., Armstrong R E. G *Med World* 1951, 74, 70
[16] Greenwald I *Bull Hist Med* 1945, 17 229
[17] Campbell J M H *J Hyg Camb* 1927, 26 1
[18] Hercus, C *Canad med Ass J* 1953 68 531
[19] Rymcki P Contribution à l'etude de l endemie goitreuse, Canton de Vaud Thesis Lausanne 1952
[20] Marine D *Ann intern Med* 1953 41 875

But in any case, if the backward areas were only brought half-way towards the best-staffed areas, the S H M O and senior-registrar problem would be solved

As I have an axe to grind, may I sign myself

S H M O (EX-SENIOR-REGISTRAR)

SPERMATOGENIC REPOPULATION OF MOUSE TESTIS AFTER X-IRRADIATION

SIR,—A single 1000r exposure of male C57 black mice shielded above the pelvis resulted in the usual depopulation of the spermatogenic tubules

Three weeks after exposure tubules appear essentially empty except for certain cells lining the basement membrane These have been called Sertoli elements by many observers Closer seriation of the preceding events reveals the following

Acute exposure to 1000r leads to death of all spermatogonia Spermatocytes continue to develop until they meet a block at or near first meiotic anaphase This block has been found to persist in the present material for at least ten days The division block leads to a restitution M1 (first meiotic metaphase) division The resulting diploid cell appears viable Groups of such cells gradually move to the basement membrane, where they take up positions beside the surviving Sertoli nuclei These restituted cells can thoroughly mimic the appearance of Sertoli units With time, and in certain tubular-cross sections, these "restituted M1 survivors" divide mitotically and give rise to a new spermatogonial layer, from which the complete cycle of spermatogenesis is gradually rebuilt

A detailed account involving autoradiography and electron microscopy is being prepared

Division of Biological and Medical Research,
Argonne National Laboratory,
Lemont, Illinois, U S A

B R NEBEL
D H DLESK

ADRENALINE CREAM

SIR,—Dr Moss (March 29) will be pleased to hear that not all the clinical trials of adrenaline cream have been so perfunctory as he suggests

In a strictly controlled "double-blind" investigation recently conducted at this and other hospitals, the analgesic effect of adrenaline cream was compared with that of two rubefacient ointments and an inert substance The two rubefacients selected were nonylic acid vanillylamide combined with the β-butoxyethyl ester of nicotinic acid, and a combination of methyl nicotinate, glycol salicylate, histamine dihydrochloride, and capsicum oleoresin These are the active principles contained in two well-known and widely used proprietary ointments

50 patients with degenerative joint disease of the spine were subjected to the trial They were thoroughly questioned, examined, and assessed at fortnightly periods before, during, and after being told to apply each ointment They received no other concomitant therapy

The results of this trial are interesting In only 9 of the patients treated was there any measurable objective improvement following the use of any one of the ointments, and in 3 of these this followed the use of the inert cream Subjective assessment showed that 21 patients preferred the ointment containing the nonylic acid vanillylamide, 11 preferred the methyl nicotinate combination, 4 preferred the adrenaline cream, and 4 the inert cream 10 patients were unable, or unwilling, to express any preference

Although, in fact, these results do not attain any strict level of statistical significance, certain conclusions may be drawn

(1) Objective improvement cannot be expected to follow the use of analgesic ointments

(2) In the conditions treated, the majority of patients experienced greater symptomatic relief from nonylic acid vanillylamide combination This was, in fact, the more effective in producing skin hyperæmia and the more irritant of the rubefacients tested, its application has been shown by Symons [1] to produce significantly higher skin temperatures than other available preparations

(3) There appeared to be little difference between adrenaline cream and the inert cream in relieving symptoms These are obviously the least effective in producing hyperæmia

One cannot, with our present lack of knowledge of skeleto-muscular physiology, attempt to draw conclusions as to the mode of action of these applications, but the impression is that the efficacy of an ointment in relieving symptoms is directly proportional to its local irritant action Why this should be so is not immediately obvious, but I feel that it is significant that several patients, when describing the change of symptoms that resulted from the use of the most potent rubefacient, stated that they "felt that it was doing most good", surely some psychosomatic explanation could be the answer

Orpington Hospital,
Orpington, Kent

P HUME KENDALL

RELEASE BINDINGS ON SKIS

SIR,—Referring to your note on this subject (April 26, p 917), I most strongly endorse the findings given, having used efficient release bindings covering torsion and forward throw for some five seasons I have never suffered anything worse than the slightest joint soreness, and neither have my skis become detached in normal skiing A reasonable mechanical sense to adjust the bindings correctly is necessary

The design of "safeties" is difficult, especially if ski-mountaineering is undertaken, it being imperative to avoid accidents under high alpine conditions I have such faith in "safeties" that I do not insure, taking into account the very high premiums

There is still extreme bias against "safeties" on the Continent among instructors and others, and the novices who need them most use them least, as the figures you quote show I can see no valid reason whatever against the adoption of properly adjusted "safeties"

Beaconsfield, Bucks

NICHOLAS DALTON

VISITING MENTAL HOSPITALS

SIR,—Throughout this country, and indeed the world over, there are people who devote much of their time and some of their money to visiting lonely patients in hospital Yet such visits, by those who are neither relatives or personal friends, are seldom permitted in our mental hospitals, where the need is greatest It is in mental hospitals that so many patients live on year after year—their relatives having died or deserted them—receiving no letters, and having no contact with the outside world Since it requires but little imagination to appreciate their loneliness, it seems to me strange that, whereas a request to visit a general hospital for philanthropic purposes is welcomed, a similar request to visit a mental hospital is likely to be turned down

Though it may be true that comparatively few would care to penetrate the somewhat bleak and grim realities of everyday mental-hospital life, I am nevertheless certain that a substantial number of good people could be found willing to do so Some authorities will say that visits by medically untrained persons are fraught with danger But the risks are largely neutralised by the fact that responsible nurses are always on duty in the wards, and also by imposing the condition that *nothing* whatever (except tobacco, sweets, books, and writing-paper) may be taken into the hospitals by such visitors After all, our visiting chaplains are not medically trained either

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[1] Symons H F B *Ann phys Med* 1958 2 174

But the advantages of visiting have already been demonstrated in practice as well as in theory I know of a Scottish mental hospital, for example, where the physician-superintendent has arranged with various local Church guilds to " adopt " the more lonely of his patients, and to give them friendship, and even an interest in life Here, once every month, a busload of guildswomen arrive at the hospital, there is chatter and laughter in the corridors, there are picnics, days at the seaside, and even days spent in the comfort of their visitor's own home

All the mentally ill are, at bottom, starving for the want of love, and for outside interest in themselves Since there are people willing to do what they can to help these patients, surely every mental hospital ought to be encouraging—indeed seeking—such help?

Edzell, Angus H G WOODLEY

RETICULOHISTIOCYTOSIS

SIR,—In *The Lancet* in 1955,[1] under the heading A Rare Disease with Features Resembling both Rheumatoid Arthritis and a Lipoid Accumulation, I referred to the case of a man which I first described with Dr W Freudenthal,[2] under the heading Nodular Non-diabetic Cutaneous Xanthomatosis with Hypercholesterolæmia and Atypical Histological Features Dr George Graham gave me frequent opportunities of observing the case of a man under his care with analogous symptoms This man ultimately died and an elaborate account of his case was published[3] under the heading A Case of Hitherto Undescribed Lipoidosis simulating Rheumatoid Arthritis I now believe that Graham's case was of exactly the same nature as that of Parkes Weber and Freudenthal, but complicated by the supervention of a sarcomatous growth and a microbic infection, which caused the patient's death The case of Weber and Freudenthal apparently subsequently recovered with considerable permanent changes in bones and joints[4] I think that " congenital development diseases " are not so very rarely terminated by the supervention of malignant growth, which complicates the diagnosis

London W 1 F PARKES WEBER

"THESE DYING DISEASES"

SIR,—Dr Vickers (March 19) advocates abolition of the venereal-diseases clinic and dispersion of its patients to other hospital departments This, from a dermatologist, is very strange syphilis is still the great imitator, and rashes appear to be the least common sign in early or late syphilis In the Services, venereal diseases and skin diseases were formerly combined, but early in the late war it was found necessary to separate them—particularly on the insistence of the dermatologists

Under Dr Vickers' scheme the following questions would arise

(1) Would a patient be able (as at present in V D clinics) to attend without an appointment and without a doctor's letter?

(2) Who would see the transient patient—e g the long-distance driver, or seaman, who carries a small travelling book (V 15 and V 44 respectively) in which all treatment given and all pathological reports are recorded Could the patients be seen immediately and by whom?

(3) Who would undertake the care of the pregnant syphilitic woman, and which department would investigate false positive Wassermann reactions? Who would be responsible for telling a patient, without confirmation, that she has syphilis—knowing the likely effect on the patient and the family, and the risk of legal action against the doctor?

(4) Who would see the cases of Reiter's syndrome—the ophthalmologist, the genitourinary surgeon, or the general physician?

(5) Which department would deal with neurosyphilitics with cardiac complications?

Investigation of the patient's social background, tracing contacts, and dealing with " case holding " until adequate treatment has been given is not the work of the several departments mentioned by Dr Vickers Moreover the V D patient prefers the confidential approach and constant sympathetic staff found in V D clinics

The success of the anti-V D scheme in Great Britain has depended largely on the coordination which the venereologist has created from the chaos which existed when so many treated venereal diseases And, whereas the returns to the Ministry as at present compiled by the venereologist are at least a good indication of the epidemiological situation of venereal diseases, under Dr Vickers' regime no return would ever be completed

The Royal Hospital, Sheffield, 1 A I MORRISON

CEREBRAL PALSY

SIR,—Although I hardly dare to quarrel with the definition of cerebral palsy proposed by such an eminent group of " interested people " in their letter of May 3, I do feel that the second explanatory footnote (which reads, " This excludes such quantitative disorders of movement as might be met with in mental defectives ") is both misleading and unjust If we are to have strict definitions about cerebral palsy let us also be clear about mental deficiency

Other " interested people ", like myself, whose work lies with patients suffering from " damage of the brain from intrinsically or extrinsically caused development disorder (occurring in fœtal life or after birth) or perinatal, paranatal or postnatal in origin " (footnote 4), do not call their patients mental defectives or think of them as such Mental deficiency is a legal term, not a diagnosis

It is a great disappointment to us that pædiatricians and neurologists continue to perpetuate, along with nearly all the rest of the medical profession, such misunderstanding They regard all brain damage severe enough to preclude educability as " mental deficiency " and an invidious distinction has grown up between cerebral palsy and mental defectiveness, whereas we know that it is quite possible for a child with cerebral palsy to be deemed, quite correctly, ineducable and, therefore, mentally defective This child is not suffering from some other disorder superimposed on his cerebral palsy, His " non-progressive brain damage " is merely more severe

In exactly the same way the child showing quantitative disorders of movement, which excludes him, by the definition, from the " cerebral palsy " group, is suffering from either brain damage which may also fit quite well into footnote 4 of the definition or from some other physical disorder—e g, metabolic He is not, however, suffering from mental deficiency

I earnestly hope for the closer integration of " mental deficiency " (sic) with general medicine, and this will not come about as fast as it might so long as the severely damaged child suffering from an obvious, clear-cut physical disorder is suddenly labelled " mentally defective " by the general hospital physician and instant dispatch to an " institution " advised

Botleys Park Hospital,
Chertsey, Surrey J M CRAWFORD

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[1] *Lancet* 1955 ii 395

[2] *Brit J Derm* 1937 30 522

[3] Graham, G, Stansfield, A G *J Path Bact* 1946 58, 545

[4] Parkes Weber F *in* MacKenna's Modern Trends in Dermatology, p 309 London 1948

TREATMENT OF ASTHMA AND HAYFEVER BY HYPNOSIS

SIR,—The article by Dr Mason and Dr Black (April 26) is of considerable interest, but attention must be called to a serious misinterpretation of results at one point.

A series of skin tests with pollen extracts performed at weekly intervals in one small area of the body (the left forearm) could not fail to produce a gradually increasing hyposensitisation of the skin of that area irrespective of whether the patient was receiving hypnotic treatment or not. The random tests on the leg gave the true picture. The statement which they make that suggestion under hypnosis directed against her hayfever and asthma symptoms only, could inhibit *selectively* the allergic or atopic reaction in different parts of the body is therefore based on false premises. In their experiment there is no valid evidence that the skin responses were altered until specific hypnotic suggestion to that effect was made. That this could occur had been clearly shown many years ago by Clarkson [1] and Marcus and Sahlgren.[2]

Further investigation of the effect of hypnosis on the allergic skin reaction would be of great interest and might help to determine the point at which it acts. Might I suggest that a fruitful line of inquiry would be to determine the effect of histamine-induced weals. If a series of histamine dilutions ranging from 1/10,000,000 to 1/10,000 is used as testing material a clear-cut endpoint will be found in the normal individual. Dilutions up to 1/100,000 will usually produce a response, beyond that no reaction can be obtained differing from control saline. This test might be carried out on a patient before and after hypnotic suggestion. Another point which might be of interest would be to determine whether the Prausnitz-Kustner reaction could be abolished in a recipient who had previously received hypnotic suggestion.

Might I suggest that for recording of reactions it would be found less cumbersome if the area of wealing is outlined directly on to the patient's skin with a ball-point pen before the 'Sellotape' is applied? A perfect transfer can then be obtained and can be kept as a permanent record for photography or other means of measurement.

Liverpool D. BLAIR MACAULAY

SIR,—When the course of a chronic illness which has proved resistant to years of conventional treatment is reversed when treated by hypnosis, this seems good evidence to both patient and doctor of the value of hypnosis. Other doctors, however, may remain unconvinced, Dr Pepys and Dr Freeman (May 10), for instance.

Hypnosis now needs to be tested by controlled studies conducted by accepted research techniques. The treatment of warts could provide satisfactory material for such a study, for photographs could provide objective evidence of the response to treatment. Hypnotic treatment could be compared with a placebo and with an accepted treatment, such as the application of CO_2 snow. Such a study could add considerably to our knowledge of clinical hypnotism. Much laboratory work is being carried out, but there seems to be little comparable serious clinical research. The B.M.A. subcommittee which reported favourably on the medical use of hypnotism [3] stressed the need for research and suggested five fields that might prove rewarding. They suggested that such research should be organised through university departments and research foundations. I trust that their advice is being acted upon and that this valuable technique of hypnosis can finally lose any stigma of quackery and become accepted as a normal medical procedure.

St Paul's Cray, Kent L. M. FRANKLIN

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1. Clarkson, A. K. *Brit. med. J.* 1937, ii, 845.
2. Marcus, H., Sahlgren, E. *Acta psychiat. neurol.* 1936, 11, 119.
3. *Brit. med. J.* 1955, i, suppl. p. 190.

SIR,—It is nearly one and three-quarter centuries since Lavoisier composed the report of the commission of the Académie des Sciences appointed to inquire into the alleged cures affected by Mesmer, who had come to Paris from Vienna in 1778 and claimed that cures could be effected by animal magnetism or hypnosis. His remarks are so pertinent to present-day reports of clinical trials and claims of the therapeutic benefits of new and old remedies that they are worth quoting in some detail:

> "The art of drawing conclusions from experiments and observations consists in evaluating probabilities and in estimating whether they are sufficiently great or numerous enough to constitute proof. This kind of calculation is more complicated and more difficult than it is commonly thought to be; it demands a high degree of sagacity and is for the most part beyond the powers of the generality of mankind. *It is on the errors in calculations of this kind that the successes* of charlatans, sorcerers and alchemists are based, and so formerly were those of magicians, enchanters and all those in general who deceived themselves or who sought to take advantage of a credulous public. In medicine, especially, the difficulty of evaluating probabilities is greater. As the principle of life in animals is an active force increasingly tending to overcome all obstacles, so Nature, left to her own devices, cures a great many diseases, and when remedies have been applied, it is very difficult to decide how much is due to Nature and how much to the remedy. So, while the multitude considers the cure of the disease to be a proof of the efficacy of the remedy, the only *inference in the eyes of the judicious is a degree of* probability, more or less great, and this probability can be turned into certainty only by a great number of instances of the same kind."

It should be well known to all practitioners that the vast majority of persons with atopic disorders, such as asthma and eczema, will recover spontaneously sooner or later. Therefore, to discover whether any method of treatment is beneficial in this group of maladies it is essential that a properly designed therapeutic trial be carried out, with adequate controls, and the results subjected to *rigorous* statistical analysis before they are submitted for publication. *It is quite unwarranted of Dr Mason and Dr* Black to draw any conclusions as to the effect of hypnosis either on asthma or the skin reactions elicited by allergens, before and after hypnosis, in their *solitary* case of asthma in a housewife (April 26).

The fact that therapeutic claims based on a solitary case can still be published reveals a serious defect in the present-day education of the medical student, and it would seem that the time has arrived when we must insist that all medical students receive a course of instruction in elementary statistics and probability theory so that they will understand more about the *design of experiments* and the statistical controls necessary to evaluate the results *of clinical and other trials*.

Such instruction should well repay the nation in the shape of a reduced drug bill, and the practitioner himself will have to read fewer uncontrolled trials and unsubstantiated statements of success with new or old methods of treatment.

London, S.E.1 E. J. MOYNAHAN

*** Dr Moynahan has perhaps misunderstood the *purpose of the report and our reason for publishing it*. Since hardly anybody now doubts that symptoms of various kinds can be modified by suggestion, a "therapeutic claim" or recommendation of the method, based on a single case, would certainly have been inappropriate. On the other hand, 180 years after Mesmer reached Paris, nobody yet knows how suggestion works. If it can (as some believe) evoke or abolish physical lesions as well as symptoms, its effects should be demonstrable most conveniently on the skin, and the observations of Dr Mason and Dr Black form an interesting complement to (for example) J A Hadfield's apparent success in raising blisters by hypnotic suggestion[1][2] and R L Moody's observations[3] of bodily changes during an abreaction under 'Evipan' narcosis As was pointed out last week, the design of their experiment was such as to allow other interpretations of the results, but flaws of this kind are not unknown in quite large clinical trials conducted under the highest auspices Single observations can be significant, provided they are correct, and they may have to be made almost by chance if, as Dr Hadfield found, the results of experiments in one "susceptible" person may not be reproducible in others Whether or not Dr Mason and Dr Black are right in their conclusions, they seem to us to provide at least a novel approach to questions which have gone too long unanswered —ED L

ABSENCE FROM WORK ON A MEDICAL CERTIFICATE

SIR,—We learn from Mr Woodhouse's letter of May 3 that employers are preferring their employees to write their own "sick notes" This is going to deprive the general practitioner of practically the last aspect of his dying art—the "certification" of illness With child-welfare clinics looking after his youngest patients, maternity services caring for his mothers-to-be, hospital clinics treating his diabetics, epileptics, and skin cases, and their follow-up clinics taking care of his only "interesting" cases of physical disease, surely he must feel that if he is to practise any medicine at all he must exchange general practice for hospital practice

Many patients pester him to see a "specialist", and are unsatisfied until they do so to the average layman a specialist means a hospital doctor Let not the general practitioner covet the interesting medical life of the hospital doctor, however, for although the public may appreciate his importance, the Ministry take a different view When speaking of registrars (the backbone surely of the hospital service), Dame Enid Russell-Smith[4] makes the astonishing remark that in the Ministry "we do not feel that the hospital doctor is necessarily ready to be in full charge of patients" I would add that hospital doctors' salaries accord with this attitude

REGISTRAR (LATELY IN GENERAL PRACTICE)

RECORDING THE HEART-RATE DURING EXERCISE

SIR,—Your Occasional Survey (May 3) draws attention to the difficulty of recording the heart-rate during vigorous exercise While the electrocardiogram (E C G) is the only suitable signal source, it is impossible to reject unwanted muscle action-potentials by simple filtering without degrading the E C G potentials themselves

We overcame this difficulty[5] by using a differential amplifier to reject in-phase signals at the input stage, leaving the E C G with only a few random muscle spikes which could easily be filtered off The T waves were attenuated in the main amplifier and any tendency to count them as well as the R waves was finally eliminated by the trigger sensitivity control rather than by the adjustable "refractory period" We have found it convenient to record heart-rate with ventilation-rate and respiratory frequency on the same strip of paper

The cardiotachometer works reliably during violent muscular movement (running uphill on a treadmill), at rates up to the maximum so far encountered (200 beats per min) and in the presence of potential interference from sparking points, relays, and treadmill motor We feel that it brings closer the "technical finality" mentioned by your contributor than any of the devices he describes

Physiology Department.
Department of Therapeutics,
Edinburgh University

W T S AUSTIN
E A HARRIS

ONE RADIOGRAPH TO EXCLUDE PLACENTA PRÆVIA

SIR,—In most cases of antepartum hæmorrhage the placenta is normally situated In a recent survey at this hospital of 130 such cases only 23 (17 7%) had placenta prævia Our aim in our paper (April 19) was to find a simple harmless method which in our hands would obviate the need for a long hospital stay in about 80% of these cases

In retrospect we found that a single lateral radiograph after the thirty-fourth week showed evidence of a normally situated placenta in 90 out of 107 cases Subsequent events confirmed that those 90 patients could have been allowed to return home with safety We would, of course, agree with Dr Reid (April 26) that a single lateral radiograph will not be infallible in excluding placenta prævia, and also think that it would be unwise to claim 100% success even with full radiological investigation It is perhaps unnecessary to stress that only the closest correlation between the radiological and clinical findings will avoid mistakes

We would point out to Mr Percival and Dr Murray (April 26) that in this series the overall error was 2 8%, and like these two contributors we have found that the errors have diminished with experience

Leicester General Hospital

J L FREER
D R CAIRNS

SIR,—For over five years I have been carrying out soft-tissue placentography using one film only and I should like to comment on the paper by Dr Earn and his colleagues in your issue of April 19 and the subsequent letters by Mr Percival, Dr Murray, and Dr Reid (April 26)

It appears to me that when soft-tissue placentography is discussed there is some confusion as to what exactly is meant by the term To me "soft-tissue placentography" means demonstrating the placenta, and with a suitable technique this can be done irrespective of the fœtal presentation I have never required the services of an obstetrician in the X-ray department for this type of examination While displacement of the presenting part is present in placenta prævia this is no guide to the diagnosis, displacement is frequently present without placenta prævia

I cannot agree with Dr Earn and his colleagues that in placentography no special skill or equipment are required With regard to equipment I consider a filter to be essential, otherwise a properly balanced film is unobtainable Having tried various filters I have found the water pillow to give the most consistent results, being flexible it moulds itself to each patient and sustains the abdomen in the true lateral position By using a sandbag the quantity of water under the abdomen of a small patient can be adjusted The radiography must be carried out with the greatest care, a repeat film should be a rare occurrence, and in this hospital all the placentography is done by the radiologists

So far I have not had Dr Reid's experience of finding a major degree of placenta prævia with a normal lateral radiograph, but lateral implantation, though fortunately uncommon,

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1 Hadfield J A *Lancet*, 1917, ii, 678
2 *Ibid* 1920 ii 68
3 *Ibid* 1946, ii, 934
4 *Brit med J* May 3, 1958 suppl p 222
5 Austin, W T S, Harris, E A *Quart J exp Physiol* 1957, 42, 126

is one that might be missed and one has to keep this possibility in mind such cases are the only ones which would require more than one film

Full details of the technique and results are to be found in the *Scottish Medical Journal* [1]

Southern General Hospital,
Glasgow R McG C CRAWFORD

NEW METHOD OF PHENOBARBITONE ADMINISTRATION

SIR,—I was surprised that Dr Pearson (April 19), in his comments on Dr O'Connor's paper (March 22), quotes the work of Butler et al [2] Butler claims that, in regard to the constancy of blood-levels produced, there is no significant difference between the administration of phenobarbitone in tablet and in 'Spansule' form I find this claim to be based, however, on most inadequate experimental evidence

Butler gave tablets of phenobarbitone at six-hourly intervals to 2 patients and measured the resulting blood-phenobarbitone levels at two, five, and nine hours after giving the first dose It is very doubtful whether, by doing only three assays to cover a twelve-hour period, he could hope to detect, with any certainty, fluctuations in these levels which might only last, for example, from ten to sixty minutes Surely, a serious study would call for assays to be carried out at least every half hour during the period of the experiment?

Science Information Department,
Smith, Kline & French Laboratories, Ltd
London, S E 5 R S FORREST

CAUTIONARY CARDS

SIR,—Your note on A New Cautionary Card (May 3, p 975) might cause some of your readers to infer that your original editorial remarks [3] went unheeded, and that our friends, the Americans, have beaten us to it once again May I therefore point out that it was largely because of your earlier remarks that this Company decided to issue special cards for distribution by clinics and consultants to patients undergoing long-term treatment with the anticoagulant 'Dindevan' (phenindione)

Two small cards contained in a transparent plastic wallet are issued One bears the patient's name and address, indicates clearly that he is undergoing treatment with the drug, and gives the name, address, and telephone number of the physician under whose direction he is taking it It is also clearly stated that this physician should be informed in an emergency and consulted before dental or surgical treatment is undertaken On the back of the card is a space for the insertion of the patient's blood-group

The second card was designed to meet the needs of patients who have been discharged from the hospital but still have to return to an outpatient clinic for regular prothrombin-time estimations and possibly readjustment of the dose This card bears columns for the insertion of the date, prothrombin time, and dose It also serves as an appointment card for the patient's next visit to the clinic

These cards have been available since last October and are being widely used by many anticoagulant clinics We have no information as to when our American colleagues introduced their cards What is important is that cautionary cards are available in Britain, and will be willingly supplied to any consultant or clinic requiring them

Evans Medical Supplies, Ltd,
Liverpool ARNOLD WORLOCK

*** We are glad to draw attention (if belatedly) to this useful British initiative — ED L

DEATH OF A BOXER

SIR,—Dr Byrom (May 10) rightly draws attention to boxing as a source of serious injury and death There must be many who share his regret that so little is done to keep this matter before the public, especially before parents The facts are plain enough and the inference to be drawn from them is important

In many games there is a risk of injury Footballers and cricketers are occasionally killed Players accept these risks freely and the rules are partly designed to keep the chance of injury low Injury, when it does occur, is accidental It is otherwise with boxing In this sport alone it is the single purpose of the boxer to defeat his opponent and the best way to do this is by knocking him out The more we know about the structure and function of the brain the more we should understand the utter folly of allowing young people to sustain repeated head injuries Postmortem studies show that petechial hæmorrhages often accompany cerebral concussion and involve a loss of nerve-cells

There is another aspect of the question which is harder to write about because of the value judgments that are involved Overt aggression expressed in a socially acceptable form is apt to arouse strong emotions The spectators of boxing experience these emotions in a manner that apparently runs parallel with the severity of the beating being taken by the loser The cries for blood and for the coup-de-grace fall ill upon the ears of a civilised community when pain and suffering are at stake There are other ways of experiencing the relief that expressing these feelings can give

Anything that can be done to inform the public will help the time when boxing will cease to be regarded as a worthwhile sport Doctors and others who work with young people might well decide where they, as individuals, stand in this matter There is much that they can do

Charterhouse,
Godalming J A WAYCOTT

SIR,—Dr Byrom's letter recalls to mind the important annotation on cerebral injuries during boxing that appeared in *The Lancet* on May 27, 1950, and a letter from me that you kindly published on June 10 of that year (p 1089) In it, I urged that a referee should not hesitate to stop a contest in which a man was being severely punished and particularly when uneven skill made a complete knockout only a question of minutes or seconds Unfortunately this relative safeguard against serious cerebral injuries is not being universally practised

In an amateur boxing contest, which was televised last week, one opponent was described by the commentator as inexperienced and having had only twelve contests, and the other one as very tough and experienced and having had over one hundred contests, most of which he had won The disparity was soon obvious in the performance, but nevertheless the referee permitted the inexperienced contestant to continue boxing after he had taken two counts of eight seconds, with the easily predictable sequence that the poor victim was very soon knocked out completely and carried to his corner by his seconds

Until otherwise competent referees acquire the courage and judgment to stop such contests earlier, and until the crowds and the contestants learn to accept such intervention as wise and humane, boxing will continue to be associated with a greater degree of risk than is necessary

I put forward similar views in a letter to the *British Medical Journal* (of Jan 8, 1955, p 102) and concluded that in spite of such preventive measures of prudency "trials of skill, endurance, and courage will still remain in very full measure for those who enter the ring in combat."

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[1] Crawford R McG C, Grieg K, Sutherland, A M *Scot med J* 1957, 2, 451

[2] Butler T C Mahaffee C, Waddell, W J *J Pharmacol* 1954, 111, 425

[3] *Lancet*, 1956 ii 1143

London, W.1 S. LEONARD SIMPSON

STRAMONIUM POISONING

SIR,—It goes without saying that we patients must pay a price for the heroic doses of stramonium used in the treatment of parkinsonism (90–120 minims of the tincture, or 3 pills, t.d.s.). In my experience that price is vomiting of a peculiar nature.

The attack is heralded by 3–5 days' obstinate constipation, associated with some rectal flatus. It begins about midnight and may awaken the patient. Starting gradually, it works up to a climax when the vomiting is copious, after which it ceases abruptly. The vomit is dark brown and contains little, if any, food residue. The most characteristic feature is the vomiting of lengths of thick mucus, obviously the result of gastritis. The attack ends with the passing of three to five motions of normal size in 36 hours.

The way to avoid this unpleasant effect of stramonium is to keep the bowels open while giving this drug.

F.R.C.S.E.

A POSSIBLE MODE OF ACTION OF INTRINSIC FACTOR

SIR,—It is a matter of great interest that the oral therapy of pernicious anæmia has been successfully achieved by Dr. Heathcote and Dr. Mooney (May 10) with a vitamin-B_{12}-peptide isolated from a fermentation of streptomyces. One must bear in mind, however, that in the initial period of the therapy a relatively high dosage of vitamin B_{12} was used and that a daily oral dose of 100 µg of the vitamin itself will produce remission in patients with pernicious anæmia.

I find it difficult, however, to agree with the statement that the effectiveness of the peptide indicates the fact that intrinsic factor probably does not exist. On the contrary, it appears that there may now be another link in the chain of a series of observations indicating the possible role of the factor itself. It could be that it is concerned in the conversion of vitamin-B_{12}-protein complexes, which in themselves are not absorbed, to vitamin-B_{12}-peptide complexes which can be absorbed. This is supported by the fact that raw liver contains vitamin-B_{12}-peptides and oral therapy with this material is successful; here again one must bear in mind the question of dosage. Moreover, a vitamin-B_{12}-mucoprotein complex has been prepared from hog gastric mucosa[1] and proved successful in the oral therapy of pernicious anæmia whilst in an impure state, with further purification, clinical activity was lost. We have shown[2] that the original impure material contained a mucoprotein, which behaved on electrophoresis very much like our own intrinsic-factor preparations. It is interesting to note, therefore, that the vitamin-B_{12}-mucoprotein complex was effective in oral therapy only when given at the same time as material which could have been intrinsic factor.

Our own intrinsic-factor preparations[2] produce remission with only 5 µg vitamin B_{12} daily and do not have proteolytic activity. The particular type of activity envisaged in the conversion of a vitamin-B_{12}-protein complex into a vitamin-B_{12}-peptide complex would therefore involve intrinsic factor as one of the components of an enzyme system and not necessarily as the enzyme itself.

One very real difficulty in relation to the above suggestion is the fact that Holdsworth[3] has prepared a protein of molecular weight approximately 40,000, which complexes with vitamin B_{12} and is capable of bringing about its absorption. The vitamin-B_{12}-binding power is only half the theoretical value and it is possible that one half of the complex molecule plays a part in the intestine in breaking down the other half to a vitamin-B_{12}-peptide.

Department of Pathology, King's College,
University of Durham,
in the Royal Victoria Infirmary,
Newcastle upon Tyne

A. L. LATNER

GENETICS AND BLOOD MORPHOLOGY IN AMAUROTIC IDIOCY

SIR,—The occurrence of vacuoles in the cytoplasm of between 5% and 20% of the lymphocytes in juvenile amaurotic idiocy was first reported by Bagh and Hortling.[4] This was confirmed by Rayner[5] who also reported similar findings in the parents and some of the siblings of patients with juvenile amaurotic idiocy.

Further data have now been collected covering all patients with juvenile amaurotic idiocy who have been admitted to hospital during 1950–56 in Sweden. Their parents, siblings, nephews and nieces, and in-laws have also been examined personally by one of us (S. R.). For each individual at least 300 lymphocytes have been studied in ordinary Giemsa-stained blood-smears.

The results, which are given in the accompanying table, indicate that lymphocytes with vacuoles are an important sign of the disease. If present in small proportions (i.e., about 1–2% in a healthy individual, they indicate heterozygosity, but their absence does not disprove heterozygosity. Neither does their presence prove it, for vacuoles in the lymphocytes may be seen in other conditions—infectious diseases and at least some of the other lipoidoses. Whether or not heterozygotes for these also have vacuolised lymphocytes is at present being investigated here.

The utility of this sign can be seen in the following case. A brother of a patient with juvenile amaurotic idiocy married

LYMPHOCYTES WITH VACUOLES IN PATIENTS WITH AMAUROTIC IDIOCY AND THEIR CLOSE RELATIVES AND IN-LAWS

Category (relationship to propositi)	No. examined	No. with vacuolisation		Average % vacuolised lymphocytes
		observed	expected*	
Homozygotes (propositi — secondary cases)	29	29	29	17·7
Heterozygotes parents of propositi	43	31	43	2·1
Normal siblings	46	18	31	1·6
Normal nephews and nieces—both parents with lym. vac.	4	3	3	1·4
Normal nephews and nieces—one parent with lym. vac.	12	4	6	2·5
Normal nephews and nieces—parents without lym. vac.	10	1	0	1·3
In-laws married to siblings	14	1†	?	1·3
No. examined	158			

*Assuming manifestation in all homozygotes and heterozygotes and a fully efficient diagnostic method.

†This individual is the mother of the family reported in the text. This family, with the exclusion of the now diseased child, also appears in the 4th row of the table.

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1. Andresen, J. G. *Acta pharm. tox., Kbh.* 1954, 10, 241.
2. Latner, A. L., Merrills, R. J., Raine, L. *Biochem. J.* 1956, 63, 501.
3. Holdsworth, E. S. *Ibid.* 1957, 66, 59P.
4. Bagh, K. V., Hortling, H. *Nord. med.* 1948, 38, 1072.
5. Rayner, S. *Acta genet.* 1952, 3, 1.

an unrelated woman Both were found to have lymphocytes with vacuoles—2% and 1 3% respectively They had five children, all apparently healthy There were no vacuoles in the lymphocytes of one child and 1 0–1 6% in three However, the remaining girl, aged 5 years, had 17% lymphocytes with vacuoles At a follow-up examination 2 years later, this girl was found to display typical signs of the disease

The investigation is continuing with examination of various control groups to assess how far this method is critically diagnostic and how it may be improved

State Institute for Human Genetics,
Uppsala, Sweden

S RAYNER
J A BOOK

STAPHYLOCOCCAL INFECTION IN INFANCY

SIR,—I refer to the annotation on this subject in your issue of Feb 1 It is there stated that it is not known how long hospital epidemic strains taken home by mothers and babies persist in the community

In 1949 I published a report on a widespread outbreak of staphylococcal infections [1] originating in maternity units which were caused by what is now known as phage-type 57 but was then referred to as type W I there reported a number of instances of long persistence of the epidemic strain in families The following is an example

Family no 1 —" Baby developed pustules when 10 days old Boils on head at 90 days Mother had boils on hips Father had boils on neck when baby four months old Grandmother living with family also had boils on face and hands The baby developed further pustules when 10 months old and the grandmother more boils on the face swabbing this family gave the following results Baby, pustule and nose, W positive, Mother, throat and nose, W positive, father, throat, W positive, Grandmother, boil and nose, W positive "

Instances are there quoted of carriage up to eighteen months

During the past four years we have had several experiences of families carrying hospital-acquired types (particularly type 81), and intermittently developing boils, &c, for even longer periods of time

Shaughnessy Hospital,
Vancouver, British Columbia

J C COLBECK

DUODENAL ULCER AND THE ABO BLOOD-GROUPS

SIR,—In 1953 Aird et al [2] demonstrated an association between the ABO blood-groups and cancer of the stomach, group A being significantly commoner in patients with the disease than in controls An increased frequency of blood-group O in patients with peptic ulcer was found also by Aird et al [3] and in patients with duodenal ulcer by Clarke,[4] and by Koster et al [5]

I have compared the distribution of ABO groups in patients with duodenal ulcer with that in healthy persons from the same localities The numbers are necessarily small, and the results can only be on the borderline of statistical significance, but individual series are often helpful, since large collected statistics of uneven accuracy may miss points of importance

Of 147 patients with a duodenal ulcer, 110 were of the same social class (Civil servants) The diagnosis was confirmed by serial radiographs The remaining 37 were all patients under the surgical unit of the Municipal Hospital of Athens, and were operated on by the same surgeon The ages of the patients ranged from 20 to 70 years

For the controls I selected 157 persons 110 were mostly friends and relatives of the patients, the rest were volunteer blood-donors registered in the blood-bank of the Greek Red Cross The patients and controls were inhabitants of Athens, but were born in different parts of Greece, and were probably representative of the whole population

In the patients with duodenal ulcer, in both sexes combined, the overall frequency of blood-group O was 42 1% and that of group A 40 1% (table I), the corresponding figures in the controls were 43 3% for group O and 42% for group A

TABLE I—BLOOD-GROUPS IN PATIENTS WITH DUODENAL ULCER

Blood group	O	A	B	AB
No of patients	62(*42 1%*)	58(*40 1%*)	22(*14 8%*)	5(*3 4%*)
Difference from % in controls	−1 2	−0 9	+2 8	+3 3

A statistical analysis of these results was made, comparing the frequency of group O in the controls and in the patients with duodenal ulcer The application of the test of independence, at significance level P=0 05, gave χ^2=0 92 This *indicates that the likelihood of a duodenal ulcer developing is no greater in group-O than in group-A individuals*

Table II suggests that group O preponderates in men with duodenal ulcer and group A in women with duodenal ulcer Similar results were found in the controls

TABLE II—GROUPS O AND A IN PATIENTS WITH DUODENAL ULCER

Sex and blood-group	Men		Women	
	O	A	O	A
No of patients	47(*44 3%*)	40(*37 7%*)	15(*36 5%*)	18(*43 1%*)

I analysed these data and found a standard deviation of 0 09 for the difference in group O between male and female Since the total number of patients was much greater than 50 I applied the test of Gauss–Laplace to the difference I found that t=0 83 and P=20 33

There is thus no real evidence of a difference in the frequency of distribution of group O between men and women with duodenal ulcer

I record my sincere appreciation of the help I received from Mr Const Athanasiadis, professor of statistics, High School for Financial Studies, Athens

Clinic of Therapeutics,
University of Athens

GEORGE PAPAYANNOPOULOS

ORAL DIURETICS

Mr JOHN H FINGERHUT, deputy managing director, Merck Sharp & Dohme Ltd, writes

" Your editorial on oral diuretics (May 10, p 1005) was noted with interest, and in particular the mention of our new drug chlorothiazide (' Saluric ') The basic N H S cost of 8 g of chlorothiazide was unfortunately incorrectly quoted This should have been 7*s* 6*d* and not 9*s* 10½*d* Your readers may like to know that the average basic N H S cost of chlorothiazide for maintenance treatment of patients with cardiac œdema is 3*s* 9*d* per week "

Medicine and the Law

Damages for Death After Penicillin

A farmer, aged 34, was known to be sensitive to penicillin, but by mistake a nurse gave him a penicillin injection and he died [1] Damages of £17,500 were originally claimed, but in view of the fact that the widow would inherit £5000 from her husband's estate, this figure was reduced to £12,500 with costs, to which the hospital board agreed

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[1] Colbeck J C *Canad med Ass J* 1949, 61, 557

[2] Aird I Bentall H H Roberts, J A F *Brit med J* 1953, i, 799

[3] Aird I, Bentall H H, Mehigan, J A, Roberts, J A F *ibid* 1954, ii 315

[4] Clarke C A *Lancet*, 1955 i, 514

[5] Koster, K H, Sindrup, E., Seele, V *ibid* 1955, ii, 52

[1] *Birmingham Post*, May 8, 1958

Obituary

JAMES HARPER

M A, M B Glasg, F R F P S

Dr James Harper, consulting surgeon in diseases of the throat, nose, and ear to the Glasgow Royal Infirmary, died on April 27

He was born in Glasgow and educated there At first he intended to become a teacher, and after graduating M A from the University of Glasgow in 1906 he went to Jordanhill Training College, but before he had completed his course there he made up his mind to become a doctor, and returned to the university to study medicine After graduating M B in 1909, he spent some years in postgraduate study abroad in Vienna, Berlin, and London, where he was a clinical assistant at the London Central Throat Hospital, the Golden Square Throat, Nose, and Ear Hospital, and the aural department of the London Hospital In 1916 he returned to Glasgow and joined the staff of the ear, nose, and throat department at the Royal Infirmary Three years later he became chief surgeon to the department

S Y, who was his assistant and successor, writes

Dr Harper's arrival on the Glasgow Royal Infirmary staff coincided with a new approach to diseases of the throat, nose, and sinuses At this time, the physician was largely replaced by the surgeon in dealing with these conditions, and Dr Harper's early pioneer work is still known to his colleagues He was, in addition, an enthusiastic teacher of his specialty and a close student of the association of infective throat, nose, and ear conditions with many aspects of general medicine Those of us who knew him found him an inspiring teacher and a keen exponent of clinical research

Dr Harper leaves a widow and four sons, three of whom are doctors

GERALD ROBINSON

F R C S

Mr Gerald Robinson, consulting surgeon to the South Devon and East Cornwall Hospital, Plymouth, died on March 20

He was born in London in 1882 and was educated at Marlborough College and Guy's Hospital, where he was awarded the treasurer's gold medal for clinical surgery in 1903 After qualifying in 1904 he held the appointments of out-patients' officer and house-surgeon at Guy's Hospital and clinical assistant at the Evelina Hospital for Sick Children He took the F R C S in 1907 and the same year settled at Plymouth in partnership with the late Dr Hughes In 1911 he was appointed assistant surgeon to the South Devon & East Cornwall Hospital During the 1914–18 war he served as a captain in the R A M C on the staff of the Fourth Southern General Hospital, Plymouth He was consulting surgeon to the East Cornwall Hospital, Bodmin, and to the Liskeard, Fowey, Kingsbridge, and Totnes hospitals He was president of the Plymouth Medical Society for a term

Outside his profession he had many interests An expert metal worker, he was a member of the Guild of Silversmiths He was also a skilful fisherman, a good shot with both shotgun and rifle—he competed at the National Rifle Association meetings at Bisley—and a keen ornithologist and wildfowler

Mr Robinson's first wife died in 1955, and he was married again in 1956 to Miss Helen Campbell MacLashan

G L P writes

Modest and retiring, and reserved almost to the point of shyness at times, Mr Robinson always avoided publicity, a trait that endeared him even more to his friends but one that was often misunderstood by those who did not know him so well There is an old saying, "A successful man is known during his lifetime but a great man is known only after his death" To be a great man and a successful man during a lifetime is surely the highest tribute that can be paid to one as deserving as Gerald Robinson

Prof GEOFFREY RAKE

E C-J writes

I knew Geoffrey Rake at two periods of his career In the first period, at Guy's Hospital in the twenties, he suddenly became a source of amazed admiration to his contemporaries As a student he was shy and retiring, though a persevering cross-country runner, and handicapped by a bad stammer His first-class intellect was slow in developing, so he had difficulty in passing his early exams The transformation came almost overnight, under the inspired and inspiring guidance of Adrian Stokes, then professor of pathology at Guy's Geoffrey shot ahead, and was soon laden with medals Success gave him confidence but did not improve his stammer, which remained an impassable obstacle to clinical practice He was obviously cut out for research, so nobody was surprised when he departed to the laboratories of Johns Hopkins

In the States—we heard years later—there was some confusion over his salary He was not the man to send out distress calls, and for a year or so he earned only a bare living wage I do not know the details, but it was a grim business that probably left a permanent mark on Geoffrey's character

In 1952 I met him again He was then director of research of the Squibb Institute in New York He had played an invaluable part, I believe, in the American development of large-scale penicillin production, in collaboration with Fleming and Florey I had met him only once or twice, at reunion dinners, since we both qualified But when I tied myself into a financial bow-knot through miscalculating the cost of living in the United States, a phone-call to Geoffrey's New York office brought his immediate and generous aid He descended on our hotel (my family was over for a few weeks), like a fairy godfather, and wafted us all away to stay with him in New Jersey

Millstone, where the Rake family lived, is a colonial township made of wood, painted a brilliant white The houses are mostly made of overlapping oak boards, like old Kent cottages, and the church is a wooden replica of the Wren churches in the Strand The Rakes lived in "Main Street"—there was one shop and (I think) two other houses in it—and Geoffrey was the mayor This was a serious appointment and Geoffrey took it seriously It seemed to us that he took everything too seriously Miraculously, he had entirely overcome his stammer But the fifteen years had changed him into a grimly determined man, with a single-minded interest in the development of the antibiotics, which he shared with his near neighbour, Professor Waksman, of Rutgers University, of streptomycin fame, with whom we occasionally commuted from New Brunswick to New York

Appointments

Cook, E H L M B Lpool, F R C S, D O M S consultant ophthalmologist, St Paul's Eye Hospital Liverpool
Edwards, J D E, M B Lpool, D O M S part-time assistant ophthalmologist, Victoria Central Hospital, Wallasey
Kelly, J A, M B, N U I, D P H deputy M O H Dover
Littler T R, M D Lpool, M R C.P part time consultant physician, Victoria Central Hospital, Wallasey
Plumley, T A, M B Lond, D P H, D Obst deputy M O H and deputy principal school M O, Eastbourne

Colonial Appointments

Alakija, O B, M R C.S, D P H P M O, Federation of Nigeria
Campbell, I D, M B Edin, F F A R C.S medical specialist (anaesthetist), Jamaica
Cochrane, J S M R C.S D A C M O, Gibraltar
McGregor Alan M B Durh, D P H, D T M & H A D M.S, Tanganyika
Norman-Williams, C M, M B Edin, D P H, D T M & H deputy chief medical adviser, Federation of Nigeria
Paull, H S, M B Brist, D P M specialist (psychiatrist), Northern Nigeria
Valentine E J, M B, D P H, T D D medical specialist (tuberculosis), Jamaica
Vassilopoulos, V P, M B Athens A D M S, Cyprus
Walter D C, M B Aberd, D C.P, M R C.P.E assistant bacteriologist, Jamaica

Notes and News

AN ALL-IN FAMILY SERVICE

The problems and needs of the family are causing concern today, but the Council for Children's Welfare and the Fisher Group, in a pamphlet[1] based on their evidence to the Ingleby Committee, point out that among all our social services there is none with a special responsibility for the family as a unit. At present different services deal with the different problems of different members of the family, and too often the underlying factor which may be causing ill health, delinquency, or even disruption of the family goes unrecognised and untreated. These independent, self-contained services tend to cause delay, duplication, and lack of continuity in the help they offer, and because each has been set up to deal with a particular need, they are usually remedial rather than preventive. The Council and the Group agree that the committees which coordinate the work of the different services of the local authorities and voluntary organisations have proved valuable, but in their view coordination can never be a substitute for a concentration of responsibility. They therefore propose that a family service should take over the existing children's departments, and extend their work from the care of deprived children to the care of the family as a whole.

The help of the proposed service would be available to any family, whether self-reliant or inadequate. It would seek to safeguard the social wellbeing of the family and offer help to the "well" family exposed to strain as well as providing early treatment for the "sick" family. It would work in close cooperation with the present health, education, welfare, and youth employment service, and it would hope to find families in need of support through school officers, teachers, and family doctors. It would have pleasant local offices which parents would be encouraged to visit for help and advice. The new service, it is suggested, might be run by a family care committee for each local authority and it would be appropriate for it to come under the general supervision of the Home Office.

The idea of offering the family more support from fewer hands is attractive, but the proposed new service would apparently still turn to the other social services for specialist help. Each time it did so, it would in effect be putting another caller on the family's doorstep. It would best justify its existence by reducing the family's need for such outside help. It would require, its sponsors believe, legislation before it could be started, and then it would be necessary to find social workers to clothe its administrative bones. In the meantime many local authorities have already arranged for some of their workers to take a special responsibility for their problem families as families, and, as Dr Scott's recent London survey[2] showed, have made at least a beginning with preventive work among them.

REWARDS AND MERIT

Speaking at the conference of the Institute of Hospital Administrators in London on May 5, Sir James Lythgoe said that in attracting staff the National Health Service, with limited and often restricted resources, would, even in normal times, and still more in times of inflation, be at some disadvantage when competing with the large flexible resources of industry. This disadvantage could be increased if the service was also encumbered with an unduly rigid code of rules and regulations, and he believed that it was especially important to give those who were running it as much flexibility and freedom of action as possible. If the service was to compete effectively for people of ability and enterprise he believed that there should be less emphasis on guaranteed uniform treatment regardless of zeal and efficiency, and greater emphasis on differentiated rewards. He would like to see less fragmentation of salary scales and greater opportunity to recognise ability by acceleration of increases within scales, more use of merit awards beyond normal maxima, and "also power to retard advancement (and use made of it) in cases of unsatisfactory performances of duties or lack of zeal. Salary scales, as they have evolved in the public services in recent years, give insufficient opportunity to reward merit on the one hand or penalise inefficiency on the other."

HOSPITALS 1948-58

Opening the same conference and the International Hospital Equipment and Medical Services Exhibition in London on May 5, Mr Derek Walker-Smith, the Minister of Health, said that on July 5 ten years ago nearly 3000 hospitals were taken over by the Ministry. Some of them were world-famous, with fine standards and traditions, but many left much to be desired. Nearly all had suffered from inevitable neglect due to the war and its economic aftermath. Many beds were closed because of shortage of staff. "Because the amount of resources that could be devoted to the hospital service had to be and remains inevitably limited, these ten years have essentially been a period of renewal and redeployment rather than of wide expansion. But it has been a fruitful period in which much progress has been made in improving the service, both from the point of view of quantity and quality. In the sphere of hospital construction and improvement we are going actively ahead in spite of economic limitations. The last few years especially have seen a gratifying rise in the amount of money available for this purpose. In money, there was been an upward curve as follows: 1955-56, £10 million, 1956-57, £13 million, 1957-58, £18 million, 1958-59, £20 million, 1959-60, £22 million. Many old hospitals have been improved and upgraded to provide a district service with a full range of specialties. The number of consultants has increased by nearly 33%—from 5191 at the end of 1949 to 6902 at the end of 1957. Between 1949 and September, 1957, the number of available staffed beds rose from 448,000 to 474,500—an increase of 6%. Much more significant and important than the rise in the number of beds is, however, the rise in the use made of them. It is an indication, at least in part, of efficiency in management that the increase of 6% in the number of available beds has been accompanied by a rise of 27% in the number of inpatients treated."

STRESS IN GENERAL PRACTICE

Last October a joint conference was held of the London faculties of the College of General Practitioners and the Society of Psychosomatic Research. We gave some account of the proceedings[1] which have now been published verbatim.[2]

MIDDLESEX HOSPITAL MEDICAL SCHOOL

Among the new English medical-school buildings will be that of the Middlesex Hospital, for work has begun at a corner of New Cavendish Street.[3] The first phase will cost all the £970,000 that has so far been raised through donations, grants, and covenants; it includes a block of five storeys to house teaching laboratories, lecture theatres for all the preclinical departments, a more spacious lecture theatre seating 400, and a physiology demonstration room of circular stepped design. This block will be complete in September, 1959, when the council hopes to have raised the £530,000 needed for the next phase—an eight-storey block containing research laboratories, common-rooms for students and staff, and a diningroom. Later still, a residential college is planned, with rooms for a third of the school's 450 students. The new buildings will be grouped round a courtyard with a fountain and flowers; they should prove much more convenient and pleasant to work in than the present cramped, scattered, and unplanned quarters.

CLINICAL PSYCHIATRIC UNIT AT SHEFFIELD

As a joint venture of the board of governors of the United Sheffield Hospitals and the University of Sheffield, a department of psychiatry has been established under the direction of Prof E. Stengel. It was started in a limited way in 1956 with a 7-bed ward unit at the Royal Infirmary and outpatients clinics at the Royal Infirmary and Royal Hospital A main clinical unit has now been provided by converting a former reablement centre at a cost of £75,000, to be met in part from the board's capital allocation from the Ministry of Health and in part from the board's endowment fund

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[1] Families with Problems. 1958. Pp. 36. 2s. Obtainable from the Council for Children's Welfare, 23 Tillingbourne Gardens, London N. 3.

[2] Scott, J. A. *Lancet*, Jan. 25, 1958, p. 204.

[1] *Lancet*, 1957, ii, 782.

[2] *The Problems of Stress in General Practice*. Supplement to the *Journal of the College of General Practitioners*, vol. 1, no. 2. London, 1958. Pp. 11. 3s. 6d.

[3] *Times*, May 9.

The unit is pleasantly situated in semirural surroundings on the outskirts of Sheffield and stands in its own spacious grounds It has 29 beds in small wards, and a treatment unit Built-in fittings include a patient/nurse call system As many of the patients will be up and about during the day, a hanging clothes locker has been provided for each patient Each ward has its own patients' sitting-room, with writing-tables, wireless, and television On the ground floor one wing has been equipped as a diagnostic and therapy centre for outpatients and accommodation is provided for a day hospital where patients can attend for treatment during the daytime, returning at night to their own homes A communal dayroom and diningroom have been included for the use of inpatients and those attending the day hospital A sliding partition between these two rooms can be opened to make a room large enough for film shows and group therapy The interior decoration has been chosen to give a calm and restful effect in wards, with a bold use of colour and design in other areas to produce a stimulating contrast A sectional hut will house the occupational therapy department at the rear of the clinic Residential accommodation has been provided within the building for medical, nursing, and domestic staff, and on the top floor rooms have been set aside for research

APPROVED NAMES FOR DRUGS

THE British Pharmacopœia Commission has issued the following new supplementary list of approved names

Approved name	*Other names*
Chlorphenoctium Amsonate	2 4-Dichlorophenoxymethyldimethyl-*n*-octylammonium amsonate (Amsonic acid is adopted as the trivial name for 4 4′-diaminostilbene-2 2′-disulphonic acid)
Chlorproguanil	N^1-3 4-Dichlorophenyl-N^5-*iso*propyl-diguanide Lapudrine is the hydrochloride
Dextromoramide	(+)-1-(β-Methyl-γ-morpholino-*αα*-diphenyl-butyryl)-pyrrolidine Jetrium, R 875
Dimethicone	A polydimethylsiloxane
Ethotoin	3-Ethyl-5-phenylhydantoin Peganone
Hydroxychloroquine	7-Chloro-4-[4-(*N*-ethyl-*N*-2-hydroxyethyl-amino)-1-methylbutylamino]quinoline Plaquenil is the sulphate
Isothipendyl	10-(2-Dimethylaminopropyl)-10-thia-1 9-diaza-anthracene Nilergex is the hydrochloride, Theruhistin is the hydrochloride
Levomoramide	(-)-1-(β-Methyl-γ-morpholino-*αα*-diphenylbutyryl)-pyrrolidine
Norethisterone	17β-Hydroxy-19-norpregn-4-en-20-yn-3-one 17α-Ethynyl-17β-hydroxyoestr-4-en-3-one 17α-Ethynyl-19-nortestosterone Norlutin, Primolut N
Pecazine	10-(1-Methyl-3-piperidylmethyl)pheno-thiazine The name Pacatal is applied to the hydro-chloride and the acetate
Perphenazine	1-[3-(2-Chloro-10-phenothiazinyl)propyl]-4-(2-hydroxyethyl)piperazine Fentazin, Trilafon
Phenactropinium Chloride	*N*-Phenacylhomatropinium chloride Trophenium
Poskine	Propionylhyoscine Proscopine is the hydrobromide
Racemoramide	(±)-1-(β-Methyl-γ-morpholino-*αα*-diphenylbutyryl)-pyrrolidine
Ristocetin	Antimicrobial substances produced by *Nocardia lurida* Spontin contains Ristocetin A and Ristocetin B
Salinazid	*N*-*iso*Nicotinoyl-*N*′-salicylidenehydrazine Nupa-sal
Sulphaproxyline	N^1-(4-*iso*Propoxybenzoyl)-*p*-aminobenzene-sulphonamide
Tacrine	5-Amino-1 2 3 4-tetrahydroacridine
Triamcinolone	9α-Fluoro-11β 16α 17α 21-tetra-hydroxypregna-1 4-diene-3 20-dione 9α-Fluoro-16α-hydroxyprednisolone Aristocort, Ledercort
Tropigline	Tiglyltropine

FRIENDS SERVICE COUNCIL

THE Council's report[1] for 1957 gives some idea of the variety of work done in Europe, Asia, and Africa—houses have been built, schools and training institutions carried on, water supplies extended, displaced villagers resettled, refugees cared for, clothing distributed The medical work of the Council has included tuberculin tests and B C G inoculations, health education, and antenatal and postnatal clinics in South Korea—where the medical programme closed in December—and the training of nurses and the building of a new tuberculosis ward at a mission hospital in Kenya The Council (Friends House, Euston Road, London, N W 1) invites legacies, donations, and covenanted subscriptions to enable it to continue its work, expenditure exceeded income by £10,786 last year, and the deficit this year is expected to be about £15,000, which will make serious inroads into its legacy reserve fund

University of Oxford

On May 1 the degree of B M was conferred on M F Burfoot

University of Birmingham

The university will hold a degree congregation on July 17 on the occasion of the annual conference of the British Medical Association in Birmingham, over which Prof A P Thomson, dean of the faculty of medicine, will preside The honorary degree of LL D will be conferred on Lieut-General Sir Alexander Drummond, the honorary degree of D SC on Dr J S Mitchell, regius professor of physic in Cambridge University, and the honorary degree of M D on Dr I D Grant, president of the College of General Practitioners

Dr Jean Mackintosh at present part-time reader in the department of pædiatrics and child health has been appointed to a full-time post in the department of social medicine for three years from July 1 She will undertake an investigation to be financed by a grant from the Nuffield Provincial Hospitals Trust into administrative problems in the public medical services particularly under the National Health Service Acts

University of St Andrews

Lord Kilmuir, rector of the university, opened a research unit for midwifery, gynæcology, orthopædic surgery, anæsthetics, and dermatology in Dundee on May 3 The unit is housed in a former students' hostel in Dudhope Terrace, and Prof R B Hunter, dean of the faculty of medicine, said that people might wonder why these buildings were being put up away from the college The reason was that in ten years they hoped to have a new medical school and hospital The research units were being started as "islands of excellence" where people could be trained to staff the new institution

Royal College of Surgeons of England

At a meeting of the council on May 8, with Sir James Paterson Ross, the president, in the chair, it was announced that Sir Russell Brain had accepted the honorary fellowship of the college

The Jacksonian prize was presented to Mr B B Milstein A Hunterian professorship was awarded to Mr J Bryant Curtis (Melbourne), and the Begley prize was awarded to Mr Robert Cohen (London Hospital Medical College)

Postgraduate diplomas and diplomas of membership were conferred on the candidates named in the report of the comitia of the Royal College of Physicians (*Lancet*, May 3, 1958, p 975) Diplomas of membership were also conferred on D L Common, Maxwell Lindsey, and A R Molyneux

Royal College of Physicians of Edinburgh

At a meeting of the college on May 6, with Dr A Rae Gilchrist, the president, in the chair, the following were elected to the membership

J B Stanton J A Simpson, K K Das Gopal Sharan A K Ganguly, J A M Joyce William Davison, W F K Morrow N S Capstick, Mohammed Siddique S K Vaish Nellie P Fernando, N W J England, T O Ogunlesi P E Goonewardena N J Shah E M Salama Keitha Corlett N A E Samaan, P J Koblenzer, Neville Berlyne, C R Maddock, J D Todd, John Stevenson, G I G Joag, D J Patel Iftikhar Ahmad, A D Cameron N H Korner, N B Sabiel, F E Udwadia A J Gazder, M W McNicol S S Rikhy, Iqbal Ahmed, P C Nag, M A Qureshy, D A Whiting B K Roy, B D Patel

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[1] Friends Service Council Report for 1957 Pp 24

Royal College of Surgeons of Edinburgh

At a meeting of the college on May 9, with Prof John Bruce, the president, in the chair, the following were admitted to the fellowship

E G Ahern, R M Anderson, M S Bansel, J S G Blair, P S Boulter, M C Deaa, W M Hefni, T V Hingorani, E A Ingram, Harold Jackson, M M A Kader, B H Kelham, J R Kirkpatrick, Phillip Lebon, W W J Liddle, W A A G Macbeth, G B McKelvie, M R Morris, D A O'Rourke, L S Parker, B C Paton, G G Powell, G L Ritchie, J W Rodwell, J B van Schalkwyk, B P Scrivener, S J Seevaratnam, M M Sinclair, Keshmahinder Singh, Lucas Souvlis, N W Struthers, J D Thompson, J C Usdin, G A Whitefield, D B B Whitehouse, W W Wilson, C I Woolf, M K A Youssef

European Association Against Poliomyelitis

The next meeting of this Association will be held at Madrid from Sept 28 to 30 Further information may be had from the secretary of the U K Committee for Poliomyelitis, Royal College of Physicians, Pall Mall East, London, S W 1

Advisory Committee on Medical Research in Scotland

The Secretary of State for Scotland has appointed the following five new members to this committee Prof Dugald Baird, Prof D M Douglas, Prof T Ferguson Rodger, Prof E J Wayne, and Dr D J Finney

Nursery School Association

This Association is holding a conference at County Hall, London, S E 1, on June 20 at 9 45 A M The theme is to be Mens Sana—the Real Foundation Further particulars may be had from Dr David Morris, 1, Park Crescent, Portland Place, London, W 1

Surgery of Leprosy

The Friends of Vellore are holding a meeting at 1, Wimpole Street, London, W 1, on Wednesday, June 18, at 5 15 P M, when Mr Paul Brand, of the Vellore Christian Medical College, South India, will speak on reconstructive surgery in leprosy

The International Children's Centre

For doctors this centre is organising a course in nutrition, to be held in Paris for four weeks from Sept 15 The course will be in French Applications should be sent to Dr Nathalie P Masse, director of studies of the centre, Château de Longchamp, Bois de Boulogne, Paris 16e

Society of Medical Officers of Health

Teaching Group—This group, which has lately been set up under the chairmanship of Prof Fraser Brockington, is to hold its first conference on June 13 and 14, at the Ciba Foundation, 41, Portland Place, London, W 1 The speakers will include Prof Thomas McKeown, Dr J M Mackintosh (future of the medical services and its implications for the teaching of social medicine), Dr C W Dixon, Dr J B Meredith Davies (content of social medicine), and Prof Alexander Mair, Dr John Burton (teaching methods) Further particulars may be had from the secretary of the group, Dr Burton, Central Council for Health Education, Tavistock House, W C 1

Medical Student Journals

Last Saturday a conference of editors of medical student journals was held at B M A House in London by the British Medical Students' Association Mr Michael Hall, editor of the *British Medical Students' Journal*, took the chair, and at the morning session talks on editing and on printing were given by Dr T F Fox and Mr John Hunter The afternoon session was opened by Mr M Cozens, of the advertisement department of the B M A, and editors and representatives of student journals then gave shorter communications In the evening members of the conference were entertained to dinner by *The Lancet*

Dr John Burton has resigned from the medical directorship of the Central Council for Health Education, and Dr A J Dalzell-Ward, who has been deputy medical director of the council since 1952, will succeed him

On Friday, May 30, at 8 30 P.M, at the Southend General Hospital, Mr Rodney Maingot will give the *Sydney Body* lecture for 1958 He is to speak on surgery in art

Colonel J B George, late R A M C, has been appointed honorary physician to the Queen, in succession to Major-General Douglas Bluett, who has retired

Dr G H Wright, of King's College, university lecturer in anatomy has been elected into an official fellowship at Clare College, Cambridge

Mr V B Green-Armytage has been promoted to be an officer of the Legion of Honour

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CORRIGENDUM—*The Treatment of Sports Injuries* Copies of this film, which we reviewed last week (p 1029), may be had, free of charge, from Smith & Nephew Ltd, Medical & Technical Information Department, Bessemer Road, Welwyn Garden City, Herts

Diary of the Week

MAY 18 TO 24

Monday, 19th

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W 12
4 P M Dr F R Keating Diagnosis of Hyperparathyroidism
WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY, St Mary's Hospital Medical School, W 2
5 P M Dr R G White Cellular Aspects of the Immune Response
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W 1
5 P M Prof A Bradford Hill Problems of Experiments in Man (First Harben lecture)
MARLBOROUGH DAY HOSPITAL, 38, Marlborough Place, N W 8
8 15 P M Dr E M *Bluestone (New York) Social Psychiatry—a* critique
MANCHESTER MEDICAL SOCIETY
9 P M *General Practice* (Manchester Medical School) Dr C V Brown All Change (Presidential address)

Tuesday, 20th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
8 P M *Medicine* Dr D A K Black, Prof Graham Bull Dr John Goodwin Clinical and Laboratory Assessment of Water and Electrolyte Disturbances
INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Dr Phyllis Wade Radiation
INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
3 P M (Hammersmith Hospital, Ducane Road, W 12) Prof J L Wright (Dunedin) Modern Management of Placenta Prævia
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE
5 P M *Professor Bradford Hill Controlled Trials of Vaccines (Second* Harben lecture)
BRITISH ASSOCIATION OF SPORT AND MEDICINE
5 30 P M (Middlesex Hospital Medical School, W 1) Mr A E H Kendall Athletes and Adaptation to Stress

Wednesday, 21st

MEDICAL RESEARCH COUNCIL, NATIONAL INSTITUTE FOR MEDICAL RESEARCH, The Ridgeway, Mill Hill, N W 7
5 P M Prof J Waldenström (Lund) The Porphyrias
ROYAL SOCIETY OF MEDICINE
5 P M *Comparative Medicine* Dr A P Donald, Dr Eliot Slater Use of Twin Studies in Research
POSTGRADUATE MEDICAL SCHOOL
2 P M Dr D G Evans Immunisation Against Poliomyelitis
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P M Dr Joseph Smart Unilateral and Localised Emphysema of the Lung
INSTITUTE OF DERMATOLOGY
5 30 P M Miss C Hodges Radiation
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE
5 P M Professor Bradford Hill Influenza and the Common Cold (Last Harben lecture)
MANCHESTER MEDICAL SOCIETY
4 30 P M *Pathology* (Manchester Medical School) Dr J E Kench Aminoaciduria

Thursday, 22nd

ROYAL SOCIETY OF MEDICINE
8 P M *Urology* Mr H E Lockhart-Mummery, Mr J D Fergusson, Mr C G Scorer Vesico-intestinal Fistulæ
POSTGRADUATE MEDICAL SCHOOL
4 P M Prof O L Wade Output of the Heart in Exercise
INSTITUTE OF DERMATOLOGY
5 30 P M Dr R W Riddell Epidemiology of Fungus Infections
INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
3 P M (Chelsea Hospital for Women, Dovehouse Street, S W 3) Professor Wright Exotics in Ectopics
HONYMAN GILLESPIE LECTURE
5 P M (University New Buildings, Teviot Place, Edinburgh) Dr J W Farquhar *The Child of the Diabetic Mother*
UNIVERSITY OF ST ANDREWS, Queen's College Dundee
5 P M Prof J T Louw (Cape Town) Observations on Cancer of the Uterine Body

Friday, 23rd

POSTGRADUATE MEDICAL SCHOOL
10 A M Mr Dillwyn Thomas Observations on the Postoperative Care of Thoracotomy Cases
ST MARY'S HOSPITAL MEDICAL SCHOOL, W 2
5 P M Dr J O Martin Relief of Fœtal Anoxia
INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
2 P M (Queen Charlotte's Hospital Goldhawk Road, W 6) Mr John Hewitt Variations on an Old Theme

The Lancet · Saturday 24 May 1958

FEAR IN HOSPITAL PRACTICE

SOME ADVANTAGES OF HOME CARE *

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M.D. Columbia

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> "The fear of death is more to be dreaded than death itself."—
> PUBLIUS SYRUS

ONE of the chief characteristics of good physical and mental health is the ability to minimise the effects of fear. As health forsakes a man, the everyday fear associated with normal living is intensified. It makes a bad situation worse and the patient needs help in dealing with it. The complicating and enervating dread in a sick man may nullify any treatment that does not take into account his mental reaction to his illness. Yet too often this is overlooked, minimised, or even disregarded.

The patient who seems apprehensive before, during, or after diagnosis or therapy (whether or not he is in the confidence of his doctor, but most often when he is not) is, for all practical purposes, under the influence of fear. Because fear, unlike worry or anxiety, both of which it includes, requires an antagonist to evoke it, the word is seldom found in the terminology of physical disease, as if the doctor were afraid that his prestige might somehow be impaired by the mention of it. But nobody has the right to be offended by the presence of fear in his patient. Illness is a humiliating experience, and the more critical the patient's condition (up to, and including, the point of dying) the more it offends his dignity. It is normal for a person to glory in his strength, and when this precious asset leaves him, he fears that it may not return, or that he may have to pay a crippling price for its return. Even irritability or impatience during illness has an element of fear in it. Courage depends on the will to regain the health that has been lost, and the sick man is fearful that he may not succeed, or be helped to succeed, in this struggle.

Fear is aggravated when the patient is kept in the dark about his condition, or when he is left too long with his own thoughts. It is by no means restricted to the literate, but may strike most heavily the less enlightened, the ignorant and the superstitious. One has to be extremely careful in distinguishing "exaggerated" fear from "justifiable" fear. Age is a factor, since older people are closer to death and very few of us can face oblivion calmly. Again, the greater the patient's weakness—and this is true at any age—the greater his fear, which will be increased, too, if there is danger of him or his family being later reduced to social dependence. The only patient who is entirely free of fear is the unconscious patient. Helplessness, inability to manage one's own affairs, and the need to be babied during illness all have their depressing effect. Vespasian remarked that an Emperor should die standing!

In contrast with physical pain fear lies beneath the surface, and too often in hospital its existence is denied or played down. Physical signs, such as pain, fever, shock (which, in some respects, is a physical manifestation of intense fear), unconsciousness, or hæmorrhage, compel a medical response. Those which can be suppressed or contained (at some cost) may go unmollified or untended though the damage which they cause may be as great, and perhaps less endurable. Illness is always a traumatic experience. It leaves its mark and sometimes this is an irreversible scar.

An analysis of fear is an easy exercise in a hospital if only because of the abundance of clinical material. In its most challenging form it is to be found in the newly admitted patient and in the one awaiting his summons to the operating-table. It follows no established psychological pattern and is aroused by any stimuli which, rightly or wrongly, are interpreted as a threat to life or comfort.

Kind Words as Therapy

Here is a serious hospital problem which must be identified early and solved for each patient. If the doctor moves, or stands still, on the assumption that his patient's mental state will somehow improve so long as his physical ailment is being relieved, the patient must bear his deprivation as best he can. To greet a new patient, or any patient at any time of his illness, with impersonal silence that may be misinterpreted as lack of sympathy, is a self-defeating kind of neglect. The doctor must bear in mind that the patient who is before him is not a cold figure, or exactly the one who was included in past statistics of the same illness.

My mind goes back to the way the late George W. Crile used to prepare a patient for thyroidectomy. He knew that the patient was his best ally in the surgical victory which he was planning, and he did everything in his power to win the patient over and put his mind at rest before operation. The busy surgeon, the impatient surgeon, the man who expects his word (even when it cannot be heard) to be taken unquestioningly as law by the patient and his fretful family, the one who deputes such intimate duties on the assumption that confidence—another antidote to fear—can be won that way, are still among us as are, indeed, their counterparts in the medical specialties. Silence can be very harmful at times, particularly when it is wielded by those who are expected to carry healing in their hands. It may well be interpreted by the disturbed mind of the patient as a sign of therapeutic weakness, and, if a mistake has been made in assigning such a doctor to him, what is he to do? As for the administration of tranquillising drugs as a substitute for the spoken word, this resembles the administration of antibiotics while neglecting surgical asepsis. Actually it may be easier to administer therapy independently of the psychiatrist for such a secondary complication as fear than for the primary physical disability, and failure to cope successfully with the disability is no excuse for leaving the patient's fear untreated. We must be on our guard lest medical negativism and the tendency to let Nature take its course should breed callousness—the callousness evident in anyone who turns his back on an apprehensive patient. You cannot help a drowning man from a distance—you must come close to him.

Every conscientious doctor can bear witness to the exhilarating effect on a patient when the kind word is spoken at the strategic moment. If a patient can be told the good news in advance so much the better. There is no need to wait for statistical evidence based on a series of cases before applying remedies which are as potent as the balm of Gilead. Those who serve the sick, must

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* Based on an address on May 13 to the Bristol division of the British Medical Association.

have insight as well as foresight, and evaluate each case psychologically, on its merits For this they need time, patience, sympathy, and cooperation from the hospital authority, as well as encouragement Their prescriptions are as valuable in overcoming the symptom of fear as in overcoming basic and original symptoms of the illness The surgeon who never sees his patient in the conscious state after an operation may have performed a mechanical job brilliantly, but the patient will be relieved of his fear only by humane reassurance and personal interest Though statistics will not help a man who is dying, kind words will do so, and they should be used liberally Enough is seldom done

In hospitals today we see growing interest in the patient as an individual—more privacy, "rooming-in" for mothers, more liberal social service, easier hospital visiting hours, more information services, rehabilitation schemes, and the like But the problem in essence is how to give each patient the comforting feeling that he has little to fear because everything known to science and humanity has been mobilised for his special benefit Where there is hope it must be stimulated, where there is no hope it must be simulated Never laugh at a placebo, emotion sometimes plays as big a role in illness as logic, and must be treated with equal therapeutic skill even if the remedy is only palliative

Hospital and Home

The situation is complicated by another kind of fear which sometimes overtakes those who look after the patient whether on their own timorous account or because of the demands which the sick man may make on their time and energy Fear is felt not only by the patient but to some extent by the doctor who prescribes for him, by the social worker who supplements his medical care with information on such subjects as fear, by the administrators of the hospital who may have difficulty in living up to its ideals, and (last but by no means least) by the worried and anxious family of the patient

Removing a patient from his own home, however modest it may be, and transferring him to a hospital where he must compete with other ill, and possibly more gravely ill, people for attention—where, since he is outnumbered, he feels himself in a minority—is not always therapeutic We must remember that every mother is a good nurse but not every nurse is a good mother When a patient enters the hospital he faces the unknown He is a stranger among strangers, exposed to them as they are to him, in all their weaknesses, demands, and variable requirements In this case it is not true that "misery likes company" The doctor's first thought, and indeed the first thought of the hospital should be, wherever his illness allows it, to keep the patient in his own home, supported by a subsidy from the community (if need be) and in any case by the continued interest and help of the hospital The impersonal, mechanical, routinised institution of collective care is more likely to arouse fear than to relieve it, and too often the fear is justified The multiple-bed open ward in hospitals is an invitation to oversight and neglect It encourages overt selectivity in a busy doctor, or one with limited interests There is wisdom in Libman's suggestion that every hospital should have a rule that a staff doctor during his rounds should sit down for at least one minute by the bedside of each patient

These are the compelling reasons which prompted me to plan and establish a modern extramural hospital service to supplement the intramural service[1] Home care controls and limits fear while respecting the dignity and essential privacy of the individual It also saves hospital beds for more intensive use by those who cannot do without them and reduces the total community bill for medical care When medical care is properly apportioned, between hospital and home, the advantages to the patient, his doctor, and the hospital are legion Lessons in individual care are learnt more rapidly and applied within the hospital proper

The hospital has reason to fear the consequences for the patient of some of its inadequacies It is too often short of staff—and particularly of intelligent, considerate, and helpful staff It is often short of vital space It deals with patients *en masse*, in open wards, and large numbers increase the chances of error It deprives the patient of privacy and subordinates him to the needs of his neighbours in the same sickroom (and outside it) It can seldom provide him with the food to which he is accustomed, or permit his relatives free entry to his bedside It must too often deny him information about his condition, for lack of time when serving large numbers and not often because it does not know what to tell him From the point of view of too many hospitals, the best patient is the one who is admitted with a quickly curable condition, accepts everything without question, and does not complain

A good home-care service based on a hospital can do much to relieve, if not to abolish, these shortcomings Furthermore it allows the hospital doctors and the family doctors to work together The family doctor holds many keys to the solution of his patient's problem, and he should have the benefit of hospital facilities (staff and equipment) in his patient's home wherever this is preferable and practicable The hospital staff is at its best with the more technical problems of medical care which require the transfer of the patient to the hospital The family doctor should be welcome on both sides of the hospital wall and be accepted as a member of the team looking after patients

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Hospitals must advance with medical and social science They must deal with their own built-in handicaps and, in doing so, help to overcome fear from whatever source We know now how this can be done The distant château-hospital fortified against intrusion belongs to the past

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[1] Bluestone, E M *J Amer med Ass* 1954, 155, 1379

" Many girls who have perfect feet at their ten-year-old examination have severe deformities by the time they reach school leaving age, many of such a degree that they may eventually require operative treatment The present day fashion of continued all day wear of shoes of a 'slip on' or 'casual' type, which must of necessity be too small so that they can stay on, or cause cramping of the toes to keep them on can during these formative years cause hallux valgus, painful bunions and curling under of the toes, sometimes of such a degree that the nails are walked on From an economic aspect only it is doubtful if in years hence the country can afford comparatively young, middle aged, and elderly women hobbling round on deformed feet The strange fact is that the young girl of today, who would laugh at a whale bone corset of Victoria days, treats her feet in the same way as her great-great-grandmother treated her waist "—Dr R G DAVIES, annual report on the school health service, Huddersfield, 1957

THROMBOSIS OF THE INTERNAL CAROTID ARTERY

SIMULATING AN INTRACRANIAL SPACE-OCCUPYING LESION

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Although thrombotic occlusion of the internal carotid artery was described almost three hundred years ago (Willis 1664), its frequency and clinical importance are only now being established, owing to the introduction of cerebral angiography and to wider awareness of the disease. In five years Webster et al. (1956) encountered 70 cases in clinical practice, whereas Johnson and Walker (1951) found only 100 examples in the literature of the preceding fifteen years, Sastrasin (1957) has surveyed graphically this increasing incidence over twenty-three years in a large neurosurgical clinic. Furthermore, Panter (1957) reports 5 cases amongst 306 cerebrovascular accidents in almost 15,000 hospital admissions during a six-year period, and Fisher (1954) has recently found 45 examples in the routine necropsy material of two years

The clinical picture of internal carotid thrombosis is now well known, but certain aspects of it deserve more detailed consideration. Thus an important mode of presentation is that which closely resembles an intracranial space-occupying lesion. We here report 5 such cases

Case-reports

Case 1.—A painter's manager, aged 39, was first admitted to the National Hospital, Queen Square, on Dec. 9, 1954, under the care of Dr E. A Carmichael (N.H. 56282) Six months previously he had been admitted to another hospital because of major seizures, headache, and abdominal pain of recent onset. He was confused, but the only neurological signs were a right extensor plantar response and an equivocal one on the left. The cerebrospinal fluid (C.S.F) pressure was 120 mm. of water, the protein content 125 mg per 100 ml , and the cell content 2 lymphocytes per c.mm The electroencephalogram (E.E.G) showed an area of gross abnormality over the left hemisphere with depression of alpha activity over the post-central region. A parietal burr-hole failed to reveal any lesion, but the C.S.F. in the left lateral ventricle contained 500 mg of protein per 100 ml and 7 cells per c.mm The blood Wassermann reaction (W.R.) on one occasion only was weakly positive, and a course of intramuscular penicillin was given. He improved somewhat, but two months later a right subphrenic abscess was detected and drained, two months afterwards a discharging abdominal sinus was still present. Two weeks before admission to the National Hospital increasingly severe headaches returned, and four days before admission he had several generalised convulsions

Examination.—The patient was drowsy and there was evidence of considerable weight-loss Apart from bilateral papillœdema, more obvious on the left, the nervous system was normal A ventriculogram was normal, but films taken twenty-four hours later showed that the right lateral ventricle was slightly larger than the left. The E.E.G suggested a deep, central lesion.

Course—On Dec. 24, 1954, it was clear that the subphrenic abscess had returned, and he was transferred for surgical treatment He was readmitted five weeks later, having had periods of maniacal behaviour necessitating retention in an observation ward. Two days before his return, a right hemiplegia and aphasia appeared and were progressive. He had gradually become comatose. He had decerebrate rigidity with bilateral papillœdema, fixed dilated pupils, variable spasticity of the limbs, and bilateral extensor plantar responses Ventriculography showed a raised C.S.F pressure and ventricular displacement to the right, indicating a large left frontal space-occupying mass A left frontal burr-hole with needle biopsy yielded only necrotic brain tissue, and the patient died twenty-four hours later.

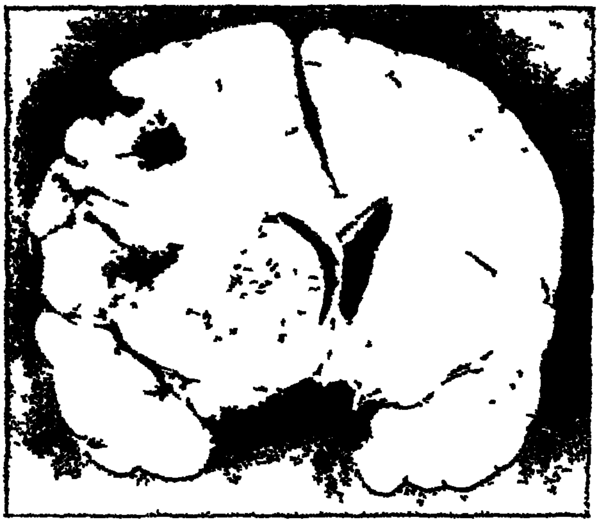

Fig 1—Case 1 brain section (viewed from behind), swollen left cerebral hemisphere.

Necropsy

The left internal carotid artery was completely blocked at its origin by an old organising clot, which, with the addition of a more recent clot, extended distally to the intracranial divisions of the vessel. At the bifurcation of the right common carotid artery an organising saddle-shaped clot was found, blocking the external but not the internal carotid artery

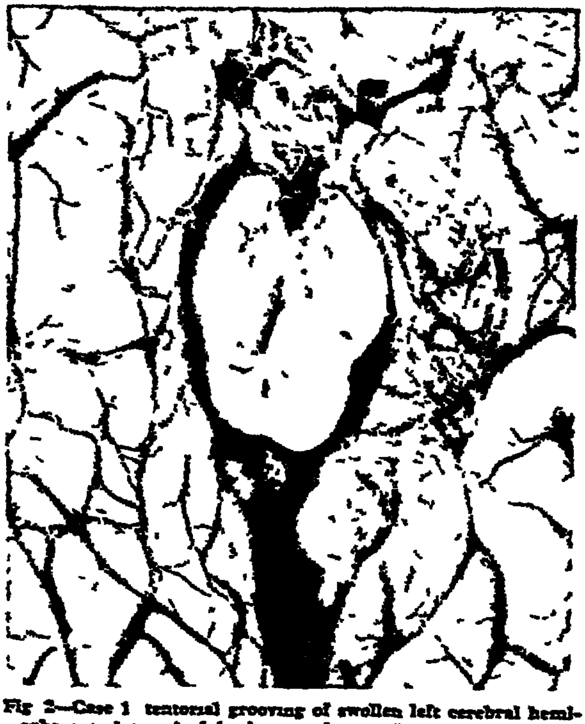

Fig 2—Case 1 tentorial grooving of swollen left cerebral hemisphere and terminal brain-stem hæmorrhage.

The vertebral arteries were normal

In the left cerebral hemisphere there was extensive pale and hæmorrhagic infarction in the distribution of the middle cerebral artery (fig 1) This hemisphere was greatly swollen, and there was evident uncal herniation (fig 2) The right cerebral hemisphere was normal

The left ventricle of the heart was moderately hypertrophied, and there was moderate atheroma of the aorta There were remnants of the subphrenic abscess

The whole clinical picture can be explained by progressive occlusion of the left internal carotid artery, terminating with complete obstruction and further infarction of the already affected left cerebral hemisphere The right external carotid artery no doubt shared in the terminal arterial obstruction, and this may have contributed to the death by compromising essential collateral channels The diagnosis of carotid occlusion, however, was made only at necropsy, and at all times a space-occupying lesion was thought to be present In view of the known focus of infection it was reasonable to postulate the presence of a cerebral abscess An angiogram, however, would have indicated the diagnosis

Case 2 —A watchman, aged 58, was admitted to the Royal Infirmary, Edinburgh, on Dec 14, 1953 A year previously he had had four "blackouts", being unconscious for ten to fifteen minutes in each For three months he had had severe intermittent left frontal headaches, and for a month weakness and numbness of the right hand and forearm, with some recovery For some months his memory had been poor and he was irritable Three times during a severe headache he had noted a haze over his left eye for about ten minutes A month before admission progressive right-sided hemiparesis developed, beginning in the face, and he became very lethargic

Examination —He was drowsy, and cooperation was limited (There was no dysphasia as he was left-handed) He had right spastic hemiparesis, right homonymous hemianopia, and bilateral papillœdema Pulsation of the carotid arteries in the neck and in the fauces appeared to be normal The blood-pressure was 135/90 mm Hg Radiographs of skull and chest were normal The C S F pressure was normal, and protein content 56 mg per 100 ml A left carotid angiogram on the day after admission showed complete occlusion of the internal carotid artery

Course —The patient became increasingly drowsy, evidence of severe brain-stem ischæmia appeared, and he died twenty-two hours after angiography

Necropsy (Dr A F J Maloney and Dr N Maclean)

There was thrombosis of the whole of the left internal carotid artery, and the clot extended into the left anterior and middle cerebral branches for about 1 5 cm The clot in the distal portion of the internal carotid artery was more recent than that situated proximally No cause for the thrombosis was found

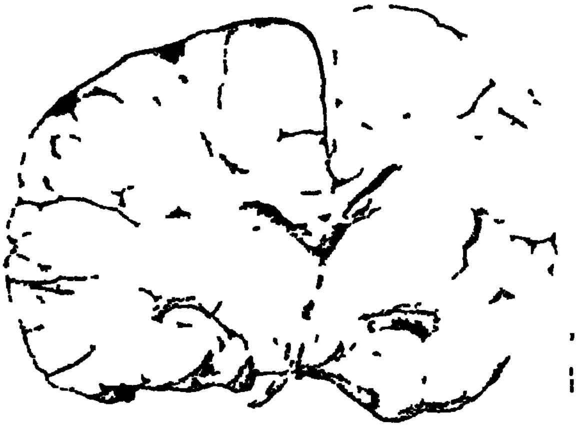

Fig 3—Case 2 brain section (viewed from behind) showing infarcted swollen left cerebral hemisphere

There was massive infarction of the left cerebral hemisphere in the territory of the middle cerebral artery, the age of the infarct varied in different parts from about two to twelve days The hemisphere was very swollen and there were secondary brain-stem hæmorrhages (fig 3)

Atheroma of the aorta and superior mesenteric artery, with old thrombosis of the latter vessel, were also found

The earlier features were thought to be due to cerebrovascular accidents, but the later picture of a progressive enlarging intracranial lesion suggested the presence of a rapidly growing neoplasm Progressive stenosis of the internal carotid artery would account for the initial symptoms, and there was complete obstruction of the lumen terminally

Case 3 —A man, aged 72, was admitted to the National Hospital, Queen Square, on July 30, 1954, under the care of Dr Michael Kremer (N H 53765) For two months he had noticed progressive difficulty in expressing his thoughts, and his wife found that he was becoming slow in his speech and did not always understand what was said to him Two weeks before admission the right foot began to drag, and the whole limb rapidly became weak

Examination —He had mild motor and sensory dysphasia The right leg was severely weak, but only slight clumsiness of the right arm could be detected Reflexes were increased in the right limbs, and the plantar response was extensor Sensation was normal Blood-pressure was 210/100 mm Hg, but the cardiovascular system was otherwise normal Radiographs of skull and chest were normal The C S F was normal The E E G showed a slow-wave focus in the left frontal region, thought to be consistent with a neoplasm A left carotid angiogram revealed obstruction of the internal carotid artery within a few millimetres of its origin, traces of dye in the ipsilateral carotid siphon suggested an anastomotic circulation An air encephalogram showed cerebral atrophy, more advanced on the left side

The picture here was of gradually progressive dysfunction of the left cerebral hemisphere, more suggestive of a neoplastic than of a vascular process, despite the patient's age and blood-pressure Efficient anastomotic channels probably prevented severe ischæmia

Case 4 —A housewife, aged 49, was admitted to the National Hospital, Queen Square, on Nov 11, 1954, under the care of Mr Wylie McKissock (N H 55679) For four months there had been obvious mental deterioration, which included memory impairment and personality changes In the preceding few weeks she had had two seizures, in one of which there were involuntary movements of the right limbs Progressive weakness of the right limbs and dysphasia then developed When she was investigated elsewhere, the only abnormality was a C S F protein of 200 mg per 100 ml

Examination —There was severe dysphasia, bilateral papillœdema, right hemianopia, and severe right hemiplegia and hemianæsthesia with corresponding reflex changes The cardiovascular system was normal Radiographs of the skull were normal The E E G showed extensive slow-wave activity arising from the left temporal region Ventriculography revealed a normal ventricular system A left carotid angiogram showed complete occlusion of the internal carotid artery at the level of the cavernous sinus

Course —The patient has remained severely incapacitated by dysphasia and a right hemiplegia

A provisional diagnosis of cerebral tumour seemed justifiable and ventriculography was carried out A carotid angiogram, however, indicated the lesion

Case 5 —A postmaster, aged 58, was admitted to the Royal Infirmary, Edinburgh, on Dec 3, 1954 Fifteen months previously he had had a cardiac infarction, and since then angina of effort Four months before admission severe left-sided headaches began, they eased after two months A right facial weakness of central origin appeared a month before admission, and two weeks later weakness and trembling of the right hand began. He also had episodes of severe, mainly expressive, dysphasia On the morning of admission he had become increasingly drowsy, and had Cheyne-Stokes respiration.

Examination —After intravenous infusion of hypertonic saline and sucrose solutions, he was not drowsy, but he had dysphasia (mainly expressive) and agraphia He had moderately severe right hemiparesis and hemianalgesia and complete right homonymous hemianopia The left pupil was dilated The cardiovascular system was clinically normal, except for a blood-pressure of 195 115 mm. Hg The C.S F was under normal pressure, and contained 21 cells (20 lymphocytes) per c.mm and 220 mg of protein per 100 ml The E.E.G was unsatisfactory owing to the patient's restlessness Left carotid angiography showed partial occlusion of the internal carotid artery at the level of the cavernous sinus, some dye had entered the basilar and posterior cerebral arteries

Course —The patient became increasingly drowsy and died five days after admission (sixty hours after angiography) with evidence of brain-stem ischæmia The lumbar C.S.F examined thirty-six hours before death was under a pressure of 160 mm water and contained 280 cells per c.mm (mainly lymphocytes), and 142 mg of protein per 100 ml

Necropsy (Dr A F J Maloney)

There were extensive severe endarteritis and periarteritis of the internal carotid arteries and of most of their branches, and of the basilar artery There was thrombosis of the termination of the left internal carotid artery, with occlusion of the anterior and middle cerebral branches

There was a recent massive infarction of the brain in the distribution of the left anterior and middle cerebral arteries, and there were terminal secondary brain-stem hæmorrhages In addition, generalised atheroma was seen, with severe involvement of the coronary arteries and aorta

The progressive nature of the illness suggested an intracranial space-occupying lesion, but the episodic features, the previous history of a cardiac infarction, and the hypertension indicated the possibility of cerebrovascular disease The internal carotid artery became completely obstructed only terminally The nature of the endarteritis was not determined

Discussion

The clinical spectrum of thrombosis of the internal carotid artery is wide, ranging from almost complete absence of symptoms, as in the patient of Willis (1664), who enjoyed " the free exercise of his mind and his animal functions ", to a rapidly fatal illness of apoplectic onset Between these extremes are found most cases

It is possible to delineate distinct clinical groups, and in the one discussed here there is a slowly progressive course simulating that of an intracranial space-occupying lesion

In Johnson and Walker's (1951) series these cases formed the second group, whereas Behrman (1954), recognising four groups, placed them in his fourth Törma and Troupp (1957) described acute, subacute, and chronic cases, and among the chronic cases were those masquerading as cerebral tumours Paillas and Christophe (1955), using the same grouping, gave the name "pseudo-tumoral" to cases in which the course was slow and progressive. Whereas Smyth (1956) thought that they formed only a very small percentage of all cases, Johnson and Walker (1951) estimated the proportion at 25% At the moment, however, there is insufficient information to indicate an incidence accurately

Thrombosis of the internal carotid artery has not uncommonly been discovered by cerebral angiography carried out in the investigation of suspected intracranial tumour (Moniz et al 1937, case 2, Riechert 1938, case 3, Sorgo 1939) There are many reports of individual cases and the patient of King (1951) is very similar to ours Wood and Farmer (1957) have reported 5 cases of cerebral softening simulating brain tumour, in 3 of which obstruction of the internal carotid artery was the cause

Pathology

The pathological processes responsible for the progressive downhill clinical course and the features of intracranial hypertension are on the whole easy to understand

The first symptoms are produced by gradual encroachment on the lumen of the internal carotid artery, resulting in the syndrome of intermittent carotid insufficiency described by Denny-Brown (1951) and others This explanation, which can also be applied to occlusive disease of other cerebral arteries (Corday et al 1953) accounts for the clinical events better than " vasospasm " or multiple emboli, though these mechanisms cannot at the moment be excluded entirely Initially the transient ischæmia does no permanent damage to the brain, but an area of infarction is eventually produced, and, as in our fatal cases (cases 1, 2, and 5), there is massive softening terminally owing to complete obstruction of the already constricted artery

When infarction of brain tissue takes place, there is swelling of the affected part, and this can be seen in cases of softening due to occlusion of intracranial arteries (Sorgo 1939, Smiley 1952, Farmer and Swanton 1955, Scarcella 1956, Wood and Farmer 1957) When it results from obstruction of the internal carotid artery in the neck or at the base of the skull, the extent of the lesion is determined by the efficiency of the collateral channels and by the distribution of arteriosclerosis, which is usually the basic arterial disease In cases 1, 2, and 5 (figs 1 and 3) there was severe swelling of the affected cerebral hemisphere, the cases of Raney (1948), King (1951), Paillas and Christophe (1955), and Berry and Alpers (1957) were similar Death is due to ischæmia and hæmorrhagic destruction of the brain-stem (fig 2) exactly comparable to that with a supratentorial cerebral neoplasm, and due to displacement of intracranial structures by an expanding mass of infarcted brain tissue (fig 2) Thus the picture—of intermittent focal brain ischæmia, followed later by infarction, and, after complete carotid obstruction, by extension of the cerebral lesion, which behaves in all respects like a growing tumour—may be indistinguishable from that of a space-consuming lesion

Clinical Findings

There are often two stages in the development of the picture firstly the progressive or intermittent appearance of focal symptoms, and secondly the features of a space-occupying cerebral lesion which usually necessitate admission to hospital The usual history is one lasting weeks or even years, characterised firstly by persistent headache, which is also a common feature in other types of carotid thrombosis, but as in case 4 headache may be absent. Focal or generalised convulsions, and progressive weakness and paræsthesiæ of the limbs on one side, mainly in the arm, now appear, often in this order, and if the dominant hemisphere is involved dysphasia will be added The defects of speech and limbs may appear in attacks with complete recovery between them, and these episodes, which presumably result from transient cerebral ischæmia, may closely simulate focal epileptic attacks Eventually permanent signs appear There is also impairment of mental state, and this too may be progressive or intermittent and may be related to disturbance of language function when the dominant hemisphere is involved

On examination in the second clinical phase, all the signs of a cerebral tumour may be discovered The patient may be drowsy and papillœdema is often present As in cases 1, 2, and 4, the papillœdema may be bilateral and at times greater on the side of the affected cerebral hemisphere (case 1), as much as 3 dioptres have been observed (Riechert 1938, case 3, Poppen and Baird 1952) Unilateral swelling of the disc, on the involved side, has been described, but in some of these cases the swelling has been an early sign of occlusion of the central retinal artery (Feiring 1954, Lamont and Brink 1956) In view of the occasional appearance of ipsilateral optic atrophy with carotid-artery thrombosis the Foster-Kennedy syndrome would be possible, but it has not been described (Fisher 1952) The signs elsewhere in the central nervous system indicate extensive cerebral damage Clearly such cases as these may closely mimic an intracranial expanding lesion, and further investigation may emphasise the similarity

Investigations

Skull radiography—If an infarcted area of brain is large enough a pineal shift may be seen (King 1951, Jefferson 1955, Droni et al 1957), but this is rare Jefferson (1955) has pointed out that radiological evidence of sellar erosion, identical with that produced by intracranial hypertension due to a tumour, can arise in patients with raised blood-pressure As internal carotid thrombosis often occurs in the presence of hypertension a further similarity is possible

Cerebrospinal fluid—Its pressure may be raised (Sastrasin 1957, case 1), but little is known of the lumbar fluid as lumbar punctures are rarely carried out in the presence of papillœdema As in our cases, the protein content and cell count of the lumbar and the ventricular C S F are often increased, because of the large area of destroyed brain tissue

Electroencephalography—Abnormalities are commoner than with other types of cerebrovascular disease (Feiring 1954), and, as in our cases, there is often a focus of abnormal electrical activity which may be mistaken for that produced by a cerebral tumour or abscess, but differentiation is usually possible if serial recordings are made Paillas and Christophe (1955) have discussed the E E G changes in detail

Air studies may indicate the presence of an intracranial mass (Elvidge and Werner 1951, Torma and Troupp 1957, case 1), but more often they are normal or show a dilated ventricle on the side of the diseased artery with a ventricular shift toward that side, indicating cerebral atrophy resulting from chronic ischæmia of the hemisphere (Johnson and Walker 1951)

Types of Space-occupying Lesion

In differential diagnosis three types of intracranial space-taking lesion must be considered cerebral neoplasm, cerebral abscess, and traumatic intracranial hæmorrhage

The confusion between internal carotid artery thrombosis and primary cerebral neoplasm during the early days of carotid angiography has already been mentioned and in addition Paillas and Christophe (1955) point out the possibility of the arterial lesion mimicking a secondary brain tumour Most authors have mentioned this diagnostic difficulty, and our cases 2–5 are examples of it

The findings most commonly simulate a malignant glioma

Carotid thrombosis may complicate an injury to the neck or head With the latter, all the manifestations of cerebral compression can be produced, and extradural, subdural, or intracerebral hæmorrhage is invariably diagnosed (Sedzimir 1955) Non-penetrating trauma of the carotid vessels may also result in drowsiness and hemiplegia, which always follow a "lucid interval" As there is often an associated head injury, or even if there is not, a diagnosis of extradural hæmatoma is not unnaturally made, whereas the responsible lesion may be thrombosis of the internal carotid artery (Schneider and Lemmen 1952, Murray 1957) Similar events may result from penetrating carotid injury (Caldwell and Hadden 1948), and case 5 of Raney (1948) offers a good example of how infarction of brain tissue due to acute internal carotid obstruction may have all the characteristics of an intracerebral expanding mass

Diagnosis

If treatment is to be effective internal carotid artery thrombosis must be diagnosed as early as possible, and certainly before complete arterial occlusion, which may produce irreversible cerebral destruction and often death Differentiation of the spontaneous type of carotid thrombosis from a cerebral neoplasm or abscess may be difficult and the two can be indistinguishable even in the presence of vascular disease elsewhere (cases 3 and 5) Palpation of the artery in the neck or tonsillar fossa is generally agreed to be of little value, and the only infallible test is carotid angiography But this is not without its risks, especially in these patients, and some have died (King 1951, Wilson 1955), the angiogram may have contributed to the deaths in our cases 2 and 5 Furthermore, Diethelm and Dontenwill (1953) have reported carotid thrombosis following angiography It is, however, possible that a less irritating radioopaque material, such as 'Thorotrast', would be justified in these cases It seems that a more innocuous investigation should be tried first Milletti (1950), Heyman et al (1957), and others recommend the estimation of retinal-artery pressures, and Fisher (1957) has reported that a bruit heard over the healthy carotid artery is of diagnostic value It has often been observed that compression of the uninvolved internal carotid artery may produce syncope (Paillas and Bonnal 1952, Shapiro 1952, case 3), and Paillas and Christophe (1955) recommend that an E E G should be made at the same time, but personal experience (P H) indicates that the test is not invariably reliable Symptoms on the unaffected side of the body may also follow compression of the healthy artery, and Parkinson (1957) has indicated the value of this test in the differentiation of carotid thrombosis from cerebral tumour An application of the technique of Meyer et al (1956), who found E E G changes in the presence of insufficiency of carotid blood-flow and a fall of blood-pressure, may also be useful Direct inspection of the vessel may, however, be necessary, and at times angiography cannot be avoided

A further diagnostic possibility of the greatest importance is occlusion of the internal carotid artery in the presence of an intracranial space-occupying lesion Thus Pauly (1954) describes a patient with the clinical appearances of a cerebral neoplasm who was shown by angiography to have complete occlusion of the ipsilateral internal carotid artery in the neck The angiogram was repeated and the vessel was now patent, indicating presumably that the initial findings were due to arterial spasm, this patient had a frontoparietal glioma Similar cases are reported by Erikson (1943) and Krayenbuhl and Weber (1944, case 19), and Gros (1955) mentions spasm of the internal carotid artery associated with a cerebral abscess Thus the angiographic demonstration of an obstructed artery in a patient with symptoms and signs of a cerebral tumour does not necessarily invalidate the diagnosis of a neoplastic or infective process in the brain The appearances of the angiographic block often permit differentiation, but further angiography (preferably by direct exposure of the artery) or air studies will be necessary in these difficult cases

Another possibility is slowly progressive internal carotid thrombosis as a complication of malignant hypertension, for symptoms and signs of high intracranial pressure together with focal neurological abnormalities would be expected Clarke and Murphy (1956) did not find an example among 190 patients with hypertension and papillœdema, but not all the necropsies included inspection of the carotid arteries in the neck

Treatment

The mortality and morbidity of internal carotid artery thrombosis are high Sastrasin (1957) estimates the mortality at 34%, of the survivors of his 65 patients, more than half had a severe neurological deficit Our approach to treatment must therefore be as active and as early as possible Nevertheless, the prognosis in many cases is determined not by the lesion of the internal carotid artery alone but also by the basic defects of arteriosclerosis and inadequate collateral channels

If possible, treatment should be carried out before complete arterial occlusion takes place, but this is only occasionally feasible, Edwards and Rob (1956) report the successful surgical handling of a stenosed artery Medical measures, such as antispasmodic and anticoagulant drugs, have not been very effective in the chronic or the acute phases of the disease, and anticoagulants are thought by some to be contraindicated in view of possible hæmorrhagic complications in the brain A surgical approach seems to be more profitable (Rob and Wheeler 1957), and Strully et al (1953) have described a patient who was at first thought to have a cerebral neoplasm but who was shown by angiography to have thrombotic occlusion of the internal carotid artery, and in whom thromboendarterectomy was successful

In the acute phase of complete arterial occlusion, therapy has unfortunately been unavailing To counter the swelling of the brain produced by infarction, bilateral subtemporal decompression has been carried out without success (Schneider and Lemmen 1952, case 2), and other measures to reduce intracranial tension have also failed to prevent death Hypothermia, as used with other cerebrovascular conditions (Lougheed et al 1955, Burrows et al 1956, Bohm et al 1957), may be more valuable, and together with the advance of arterial surgery may some day reduce the mortality and morbidity of this disease

The importance of considering thrombosis of the internal carotid artery when dealing with a patient manifesting the features of an intracranial space-occupying lesion is obvious, and the earlier the diagnosis can be made the more effective is treatment likely to be

Summary

Among the many clinical pictures produced by occlusion of the internal carotid artery is that of an intracranial space-occupying lesion

5 illustrative cases are reported, in 4 cerebral neoplasm had been diagnosed, and in 1 cerebral abscess

The early symptoms are due to carotid-artery insufficiency, and the syndrome of intracranial hypertension is produced by the area of brain softening and surrounding œdema which appear eventually

Symptoms and signs, as well as radiographic, C S F, and E E G abnormalities, may be identical with those due to a space-occupying lesion, and certain differentiation can be made only by carotid angiography

An incorrect diagnosis of cerebral neoplasm, cerebral abscess, or traumatic intracranial hæmorrhage may be made in the presence of carotid-artery occlusion

Treatment, to be effective, must be early, operation on the artery seems to be the only hopeful possibility

We have great pleasure in thanking Prof Norman Dott and the medical committee of the National Hospital, Queen Square, for kindly allowing us to publish the clinical and pathological material

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EFFECT OF CERTAIN DIETARY OILS ON BILE-ACID SECRETION AND SERUM-CHOLESTEROL

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THE serum-cholesterol level is raised by most fats of animal origin, but is lowered by many highly unsaturated oils from vegetable and marine animal sources (Frishley et al 1955, Ahrens et al 1955, Bronte-Stewart et al 1956) The object of the present study was to identify the mechanism or mechanisms by which these unsaturated oils lower the serum-cholesterol Gordon et al (1957a, 1957b) showed that the feeding of sunflower-seed oil increased the excretion of bile acids in the fæces—to an extent that would fully account for the cholesterol leaving the circulation Hellman et al (1957), using ^{14}C-labelled cholesterol, have shown increased fæcal elimination of the radioactive material on feeding corn oil There is little doubt (Siperstein et al 1952, Bergstrom and Norman 1953, Siperstein and Chaikoff 1955, Siperstein and Murray 1955) that cholesterol is excreted mainly as bile acid, both in the rat (taurocholic acid), and man (glycocholic acid) In the experiments to be described, three patients with complete bile fistulæ were studied, the bile-acid output being followed during manipulation of the serum-cholesterol by administration of various fats and oils

Methods

The clinical features are summarised in table I No patient had clinical or biochemical evidence of disturbed liver function, nor was there overt infection of the biliary tract

On and after the third postoperative day, they received a basal diet yielding 2000 calories and containing 75 g protein and 5 g fat The common bile duct was drained through a T-tube, this was indicated after exploration of the duct, and in case 2 the dilated sphincter of Oddi was splinted by a long-limbed T-tube Wangensteen drainage was used in cases 1 and 2 but was probably unnecessary, for collection by siphonage in case 3 was entirely adequate The postoperative course of the patients was satisfactory, and no deleterious effects resulted from this regime The fistulæ were thought to be virtually complete, because little or no bile acid was detected in the fæces, and the stools were pale Blood was drawn at intervals of about 48 hours, at 9 A M Fat absorption, as expected, was impaired by the existence of bile fistulæ, absorption was 80–90% during fat feeding , In animals with bile fistula, 65–75% of fat is absorbed (Pessoa et al 1953)

Bile was collected in 24-hour batches, with thymol as a preservative, it was stored at −15°C and worked on within 4 days Aliquots of 1 ml were saponified in sealed ampoules at 120°C for 4 hours, by means of 2 ml of 2 *N* sodium hydroxide The unsaponifiable fraction was extracted with petroleum ether (40–60°C boiling *point) and the cholesterol content determined by the Liebermann* Burchard reaction The aqueous phase was then acidified, congo red was used as the indicator Fatty acids were removed by petroleum ether extraction, and bile acids extracted with four 4-volum quantities of ether, the ether extract was washed with 0 2 volumes of water, then taken to dryness In this form it was stored at −15°C until analysis was completed Bile acids were identified and determined by Mirvish's (1958) quantitative modification of the reversed phase column-chromatographic procedure of Sjövall (1953) In this laboratory the overall procedure has given 85–97 5% recoveries of cholic acid and 82–100 2% recoveries of deoxycholic acid The chromatographic system does not resolve deoxycholic from chenodeoxycholic acid

CLINICAL FEATURES OF THE THREE PATIENTS

Case	Age	Sex	Race	Operation	Interval between operation and first basal observation
1	30	F	African	Cholecystectomy and choledochotomy for stone in common duct	5 days
2	36	M	European	Sphincterotomy for relapsing pancreatitis	8 days
3	68	M	Coloured	Cholecystectomy and choledochotomy for stone in common duct	5 days

Serum-cholesterol was determined by the method of Abell et al (1952) as modified by Anderson and Keys (1956) The procedure of van de Kamer et al (1949) was used in measurements of fæcal fat

Sunflower-seed oil, of refined grade, was used from a single batch, the iodine value was 135, and the Liebermann-Burchard chromogen in the unsaponifiable fraction was equivalent to 751 mg cholesterol per 100 ml Coconut oil was hydrogenated

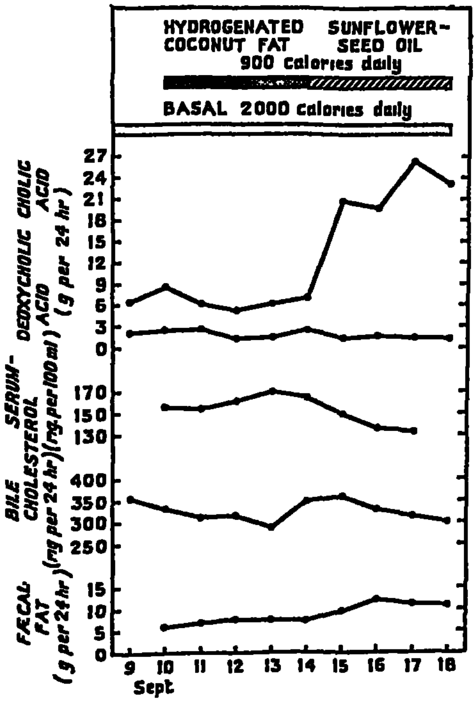

Fig 1—Case 1 Response to hydrogenated coconut fat followed by sunflower-seed oil

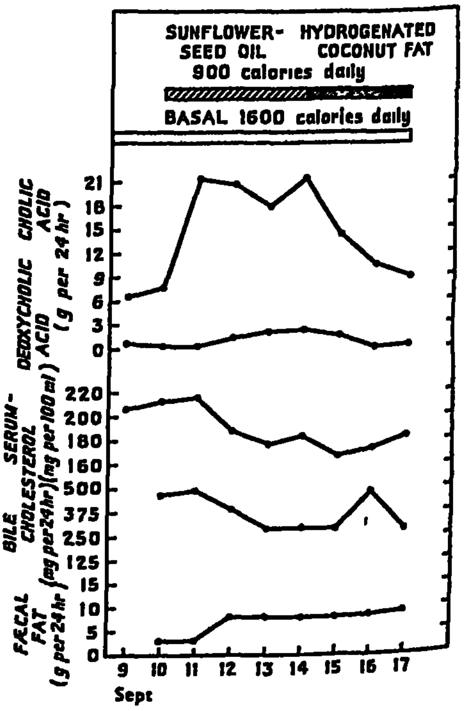

Fig 2—Case 2 Response to sunflower-seed oil followed by hydrogenated coconut fat

to an iodine value of 6, and contained 303 mg per 100 ml of similarly measured sterol The oils were administered uncooked, in divided doses A preparation of cotton-seed oil for intravenous use ('Lipomul', Upjohn), emulsified with 'Pluronic F68' and soybean phosphatide, was also used This oil had an iodine value of 115 On intravenous administration the emulsion lowers the serum-cholesterol (H Gordon, unpublished observations)—a property not shared by a comparable oil-free solution containing the emulsifying agent. Unfortunately no similar preparation of a saturated fat was available

Results

Case 1—Hydrogenated coconut oil did not raise the serum-cholesterol level, and had no effect on the composition of the bile. Sunflower-seed oil given for 4 days lowered the serum-cholesterol significantly and produced a fourfold increase in the cholic-acid secretion Deoxycholic-acid and bile-cholesterol output did not vary consistently The fæces were virtually bile-free. The increase in cholic-acid secretion began on the day the oil was introduced, and thus preceded the fall in serum-cholesterol (fig 1)

Case 2—The order in which the oils were administered was reversed in this experiment, the response was essentially similar (fig 2), except for a moderate rise in the deoxycholic-acid (— chenodeoxycholic-acid) peak When sunflower-seed oil was replaced by hydrogenated coconut oil, the cholic-acid secretion fell steeply but did not reach the basal level in 3 days

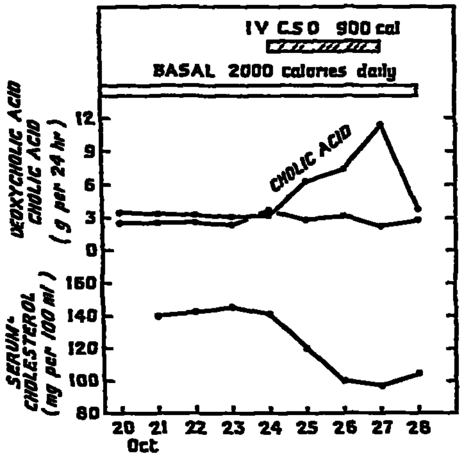

Fig 3—Case 3. Response to infusion of cotton-seed oil (I V C.S O)

Case 3—Intravenous infusion of cotton-seed oil was at least as effective as oral sunflower-seed oil in lowering the serum-cholesterol, cholic-acid output was increased (fig 3)

Discussion

This investigation was based entirely on transient-state observations, being concerned with the phenomena associated with a *changing* serum-cholesterol The establishment of bile fistulæ increases bile-acid synthesis in rats (Eriksson 1957), a plateau being reached in 3–4 days The present experiments were internally controlled and the basal observations began not less than 5 days after operation. Diet-induced fluctuations in the serum-cholesterol could theoretically be due to variations in its rate of synthesis, absorption, deposition, excretion, or catabolism, in the process of cholesterol "trapping" (Byers and Friedman 1955), or in more than one such mechanism An earlier communication (Gordon et al. 1956) described our failure to demonstrate significant changes in fæcal Liebermann-Burchard-reacting sterols during manipulation of the serum-cholesterol by dietary means, and our demonstration of increased fæcal bile-acid excretion during feeding of sunflower seed oil Fluctuations in fæcal sterol excretion, in fact, correlated best in that study with the dry weight of fæces, and were conditioned by the dietary phytosterol content.

Ingestion of unsaturated oils does not suppress cholesterol absorption (Karvinen et al. 1954) Nor does it reduce cholesterol synthesis; evidence from in-vitro studies using labelled substrates is to the contrary (Merrill 1958) In the light of the present experiments as well as by exclusion, the hypothesis is submitted that certain vegetable oils (administered orally or intravenously) reduce the serum-cholesterol by a mechanism which involves accelerated catabolism of cholesterol to cholic acid. Siperstein et al. (1952) and Siperstein and Murray (1955) were able to recover 95% of the radioactivity of labelled cholesterol from the fæces, of which over 80% was in the bile-acid fraction, the remainder in neutral material.

Conversely, the elevation of serum-cholesterol levels by hydrogenated coconut fat was not associated with reduction of bile-acid output, measured directly in two people with fistulæ or indirectly in the fæces of six normal ones (Gordon et al. 1957a, 1957b), though Salomon (1926) described a rise in bile-cholesterol on feeding butter This is somewhat at variance with the results of Hellman et al. (1957) in a patient with hypercholesterolæmia Using cholesterol-4-^{14}C, they found that butter oil increased the serum-cholesterol and reduced the fæcal excretion of "cholesterol and its end products", corn oil had the reverse effects These workers inferred an intestinal excretory mechanism for the regulation of the serum-cholesterol Kinsell et al (1958) were unable to detect reciprocal changes in the serum-cholesterol and the fæcal-sterol excretion on feeding a variety of preparations containing unsaturated fatty acids The findings in the present study favour a catabolic mechanism for the action of some oils in lowering the serum-cholesterol, but point to an unrelated mode of action for hydrogenated coconut oil in elevating the level of this sterol It is widely held that saturated fats increase the synthesis of cholesterol from acetyl coenzyme A, which arises from β-oxidation of fatty acids Fasting depresses cholesterol synthesis (van Bruggen et al 1952), and feeding of fat increases the rate of incorporation of ^{14}C-labelled acetate into cholesterol, simultaneously decreasing its conversion to glycogen and fatty acid (Whitney and Roberts 1955)

Quantitative considerations indicate that far more bile acid is produced during oil feeding than is necessary to account for the disappearance of cholesterol from the circulation. The inference is either that cholesterol is being mobilised from the tissues, or (more probably) that cholesterol synthesis is increased during administration of oil Increased synthesis from acetate has been demonstrated in liver slices from animals previously fed on cotton-seed oil (Whitney and Roberts 1955) An analogy may be drawn with hyperthyroidism, where there is a tendency to a low serum-cholesterol despite increased cholesterol synthesis (Kurland and Lucas 1955) Weiss and Marx (1955) have shown in animal experiments that thyroid hormone stimulates the degradation of cholesterol to acid derivatives

Summary

Bile-acid excretion has been studied during the administration of various types of fat, to three patients with complete bile fistulæ

Sunflower-seed oil (by mouth) and cotton-seed oil (intravenously), which are both highly unsaturated, produced a remarkable increase in the rate of cholic-

acid secretion, which preceded the fall in serum-cholesterol On the other hand, a saturated fat (hydrogenated coconut oil), did not affect the bile-acid output but raised the serum-cholesterol These findings support the hypothesis that the mechanism by which the serum-cholesterol is reduced by certain vegetable oils involves accelerated catabolism of cholesterol to cholic acid

Sincere thanks are due to Dr S Mirvish for allowing access to his analytical method before its publication, to Prof J F Brock and Prof L Eales for helpful criticism and encouragement, and to Prof J Louw, Mr D J du Plessis, and Mr G Sacks for making patients available for these studies Messrs Merck & Co provided samples of bile acids

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HYPOTHERMIA BY INTERNAL COOLING IN MAN

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In 1954 a new method of lowering or raising body temperature in animals and man by introducing cold or warm water inside an intragastric bag was described (Khalil and Mac Keith 1954) In September, 1956, at the second European Congress of Cardiology, a series of experiments was reported where deep hypothermia in dogs was induced by a continuous flow of cold water through an intragastric water balloon, and the term " internal cooling " was suggested for this new and simple method

In the two cases at Alexandria University Hospital reported here, this method was used in neurosurgery in man The apparatus used was the same as that which I have been using for dogs, modified to make it more compact, easier to manage, and generally more suitable for a hospital operating-theatre

Apparatus

The apparatus (fig 1) consists of a water tank N, of 10 litres capacity, which can be either cooled by means of a cooling coil D attached to a compressor, or warmed by means of an electric resistance coil P Both coils are immersed in the water inside the tank The temperature of the water is controlled by means of two thermostats—R for cooling and R_1 for warming The water tank is surrounded by a thick cork jacket which provides temperature insulation

A suction water-pump F sucks the water from the intragastric balloon into the water tank N, and, since the tank is hermetically sealed, automatically drives an exactly equal volume of water to the balloon In this way, the volume of the balloon remains constant Two air-traps G and K are included in the circuit—one G just before the suction-pump and the other K between the tank and the balloon—to prevent air from entering the balloon or the pump

A graduated 5-litre jar H, with an attached sphygmomanometer pump and a bottom tap T, lies above the tank It is connected to the tank by a T-piece Tap T is opened only while filling or emptying the balloon A (Palmer) flow-meter C is also included in the circuit, between the balloon and the pump The screw-clamps S and S_1 are applied to the thick rubber tubing leading to and from the balloon They are used to clamp the rubber tubing while the empty balloon is being introduced into the stomach, to prevent water from leaking into it at that time A special metal junction M is designed to allow to-and-fro currents through the tubes A and B leading to and from the intragastric balloon, the tubes being made of 'Porges Neoplex', 1 0 metre long The outer tube should be 1·0 cm in diameter and the inner one 0 6 cm The intragastric balloon itself is an ordinary condom—preferably two, one inside the other, in case one should accidentally leak A thermometer is immersed into the air-trap K to register the temperature of the inflowing water The whole apparatus is fitted inside a suitable stand with wheels to allow rapid transport

Operation of the Machine

The tank and all the tubing and air-traps are filled with water from jar H The intragastric water balloon is then tested by distension with water, which is done by applying pressure in the jar H through the sphygmomanometer pump The balloon is then emptied by switching on the suction water-pump and clamping the rubber tube at S_1 The suction-tube is then also clamped at S, and the tap T closed and the pressure in jar H released After insertion of an intratracheal tube, the balloon is introduced into the stomach through the mouth It goes with ease

When the intragastric balloon is in situ, both clamps (S and S_1) and tap (T) are opened and pressure applied in jar H to fill the balloon to the required volume as shown by the graduations on the jar When the balloon is full, the stomach should be palpated through the anterior abdominal wall to see that it is not unduly tense Tap T is then closed and the pump switched on Any air still remaining in the circuit will immediately be trapped in jars G and K as the water circulates The thermostat of the water-cooler unit is adjusted to the range between 5° and 7°C and the rheostat of the pump so adjusted that about 10 gallons (45 5 litres) of water passes per hour, as indicated by the flow-meter In this way 0 75 litre of cold or warm water will circulate through the balloon per minute The intragastric balloon should never be filled with more than 1 5 litres of water The arrangement by which the balloon receives only a volume of fresh water equal to what has been withdrawn will keep the volume of the balloon constant throughout the cooling or rewarming procedures, without any risk of overdistending the stomach

If the rate of cooling the body is more rapid than is desired, the volume of the balloon is reduced by clamping the rubber tube at S and opening tap T, the water will then be diverted to the jar instead of returning to the balloon When the required volume is reached, tap T is closed and clamp S_1 is released The same procedure should be repeated whenever the volume of the bag should be changed as judged by the rate of cooling or rewarming the body

When rewarming is indicated, the warming unit with its thermostat is switched on instead of the water cooler The circulating water will then be gradually warmed according to the adjustable thermostat, but its temperature should not rise more than 10 C above the rectal temperature, and should never exceed 40°C

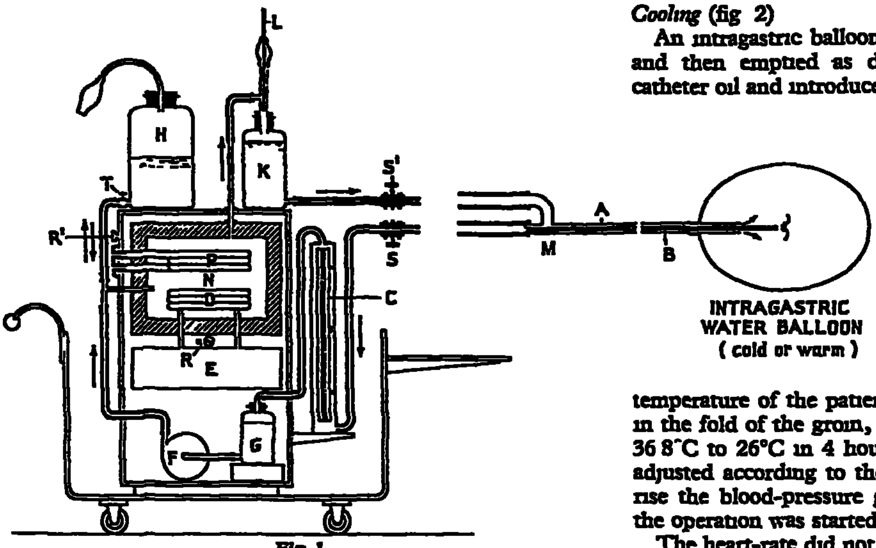

Fig 1

Case-reports

Case 1 —An adult was admitted to the neurosurgical unit, Alexandria University Hospital, with a large swelling on the vault of the skull and signs of bilateral pyramidal-tract involvement The symptoms had started three years previously and had been progressive Arteriography revealed a large parasagittal meningioma of the size of an orange

The operation was performed by Dr B Vlahovitch and Dr S Boctor Anæsthesia was conducted by Dr H Nassar and Dr W Narshy

Premedication

The patient was prepared with chlorpromazine 25 mg and promethazine 50 mg at 2 A M , this was repeated at 6 A M 1 mg atropine was given at 8 A M Anæsthesia was induced with sodium thiopentone. An endotracheal tube was introduced and its cuff inflated Anæsthesia was maintained by nitrous oxide and oxygen

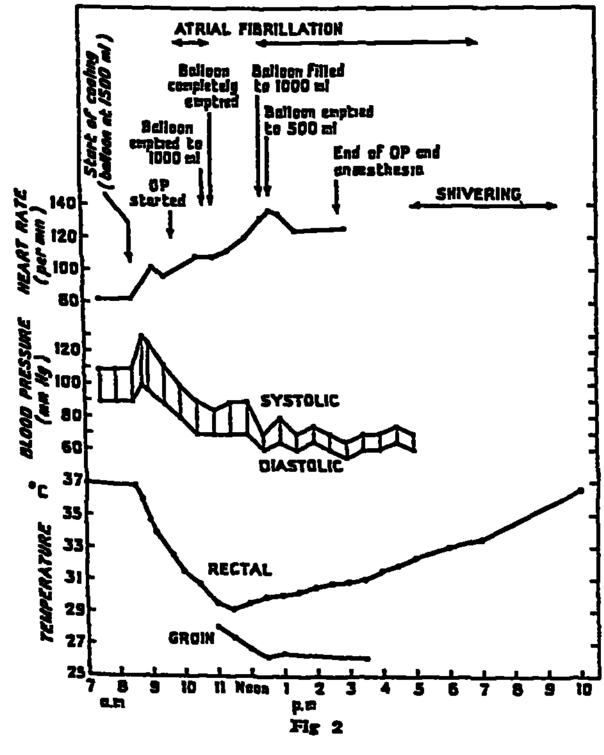

Fig 2

Cooling (fig 2)

An intragastric balloon, which had been tested beforehand and then emptied as described above, was smeared with catheter oil and introduced with ease into the stomach About 1 5 litres of water was pumped into the balloon from jar H, which was then isolated by closing tap T The stomach could be felt easily through the abdominal wall and was not unduly tense The patient was then put in the semi-sitting position for the operation Cooling was started at 8 30 A M by switching on the pump and the cooling compressor The temperature of the circulating water dropped to 5°C in 10 minutes The temperature of the patient was recorded both by rectum and in the fold of the groin, the groin temperature dropped from 36 8°C to 26°C in 4 hours (fig 2) The rate of cooling was adjusted according to the surgeon's request After an initial rise the blood-pressure gradually declined, beginning before the operation was started

The heart-rate did not undergo a corresponding drop This was probably because of the chlorpromazine and atropine premedication, in addition to the rather large blood-loss during the removal of the angiomatous tumour Atrial fibrillation began at 10 A M , when the rectal temperature was 31 5°C, and disappeared when cooling was stopped and the bag emptied at 11 A.M It recurred at 12 30 P M and remained till 7 P M , the rectal temperature then being 33 5°C This may have been another cause for the tachycardia

Operation

The operation was started when the rectal temperature was 32 2°C, 75 minutes after the start of hypothermia, it took 5 hours, ending at 2 45 P M During the latter half of the operation, cooling was started again by filling the balloon with 1 0 litre of circulating water for 10 minutes, and then maintained at a slower rate by keeping only 0 5 litre circulating This was done on the surgeon's request to retard spontaneous rewarming Otherwise, rewarming was left to take place spontaneously Anæsthesia was stopped as soon as the operation was completed The patient became responsive soon afterwards, and began to talk within an hour of the end of the operation During the rewarming period mild shivering began when the rectal temperature reached 32°C and continued until it reached 36°C

Postoperative Course

This was uneventful Next morning there was no epigastric tenderness, even on deep palpation and pressure The patient asked for food at lunch-time but was given fluids only, including milk. There was no vomiting Solid food was started on the third day

From the clinical point of view the result was very satisfactory The patient regained considerable motor power in his affected limbs within the next few days

Case 2 —A man, aged 42, was admitted to hospital with severe frontal headache, mental changes, and blurring of vision. On examination there was primary optic atrophy on the left side and severe papillœdema on the right side (Foster Kennedy's syndrome) Arteriography showed distinct shift of the left anterior cerebral artery to the right, suggesting a tumour of the left frontal lobe

Operation

This was carried out after induction of hypothermia to 32°C, by the same technique as in case 1 There was no arrhythmia, and the heart-rate dropped from 110 to 70 A left frontotemporal flap was turned The lateral ventricle was tapped to diminish the increased tension Localised frontal lobectomy was carried out exposing a dark reddish tumour that extended posteriorly under the anterior horn of the left lateral ventricle and around the left optic nerve and tract reaching the hypothalamic area The major part of the tumour was removed, leaving only the deep infiltrating part in relation of the internal capsule

Postoperative Course

The patient did well, and 5 days after the operation he was on full diet Clinically the result was satisfactory

Discussion

The advantages of internal cooling, compared with surface cooling or extracorporeal blood cooling, have been discussed elsewhere (Khalil and Mac Keith 1954, Khalil 1957a, b)

An apparatus for application of internal cooling has been described (Barnard 1956), but the apparatus described here has several advantages

Instead of pumping water into the stomach, the pump sucks the water from the balloon to the tank, the same volume of fresh cold water automatically passing from the water tank to the balloon It is impossible to overfill the stomach

The volume of the balloon can be adjusted at any moment to the required volume with greater ease

A flow-meter is included in the circuit By this means the rate of flow of water through the balloon can be controlled This is particularly useful in the shift from cold to warm water, when the rate of flow should at first be slow in order not to damage the gastric mucosa

Air-traps are included in the apparatus This is considered essential for the smooth performance of the pump and to prevent air from getting to the balloon

The action of the apparatus can be changed from cooling to rewarming at any moment Accordingly

(*a*) If, during the induction, serious cardiac arrhythmias appear, change to rewarming is possible

(*b*) After the operation is completed, the patient can be rewarmed to 35–36°C, the blood-pressure will then rise, and any bleeding-points can be noted and ligated before the field of operation is closed

(*c*) In cardiac operations the surgeon can perform the critical part of operation after rewarming has been begun by internal warming The myocardium will then be colder than the blood supplying it, and will presumably get the oxygen it demands more easily than during the cooling period (Barcroft and King 1910) The heart-muscle will then probably be less irritable to touch and other surgical insults than it is where the heart is hypothermic from other techniques Work is in progress in dogs to test the advantage of this procedure

Hypothermia by internal cooling presents advantages, and it is hoped that the simplicity and safety of this method will lead to its being tried in other indications for hypothermia Construction of the machine described here should be within the capacity of any good firm of engineers

Summary

An apparatus for giving a continuous flow of cold or warm water through an intragastric balloon is described

Two cases in which intracranial tumours were removed surgically under hypothermia by internal cooling are reported The first patient was cooled to a rectal temperature of 29°C and the second to 32°C

The method proved simple, easy to manage, and very effective—so much so that it was necessary to keep the intragastric balloon only half-filled to avoid too rapid cooling Both patients had an uneventful postoperative course

This method could be used in major neurosurgical and cardiac operations and in other indications for hypothermia

I thank Prof M L Dowidar, head of the department of surgery, Dr B Vlahovitch, and Dr S Boctor for permission and facilities to conduct this work in the department of surgery, Alexandria University, Dr H Nassar and Dr W Narsby for their help and cooperation and for conducting the anæsthesia, Prof M Naim for his encouragement and guidance, Mr S Mikhail for his valuable technical assistance, and Dr R C Mac Keith for correcting the draft of the paper and for his help in many other ways

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INFLUENCE OF LIGHT ON THE HYPERBILIRUBINÆMIA OF INFANTS

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In the first two weeks of life a raised serum-bilirubin level from any cause may lead to kernicterus In those who have died, necropsy has shown staining by bilirubin of certain cells in the central nervous system, principally in the basal ganglia The mechanism of this change is unknown, but there is evidence that it may be caused by an inhibitory action of excessive bilirubin on essential cellular respiratory activity

Day (1954) showed that oxygen uptake of rat brain is significantly reduced in the presence of bilirubin 20 mg per 100 ml, but that no such inhibition is found with biliverdin Zetterström and Ernster (1956), working with liver mitochondria, showed that bilirubin at a concentration of 20 mg or more per 100 ml exerts a powerful uncoupling effect on oxidative phosphorylation Lathe and Walker (1957) show that the livers of the newborn cannot conjugate bilirubin, which is unexcretable, to the glucuronides of bilirubin, which are excretable—the necessary enzymes being absent or deficient

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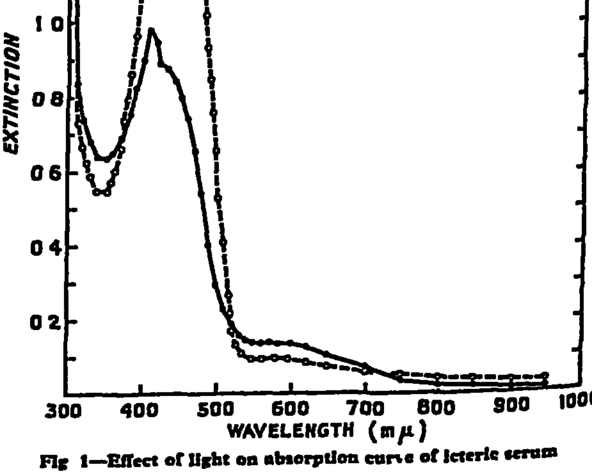

Fig 1—Effect of light on absorption curve of icteric serum

Mollison and Cutbush (1951) showed that the incidence of signs of kernicterus increases as the concentration of serum-bilirubin rises above 20 mg per 100 ml, and that below this figure ill effects are rare The prevention of a high level of serum-bilirubin, or the destruction of this substance, or its removal from the blood-stream, will prevent kernicterus This has hitherto been achieved by replacement transfusion Where experienced staff and good laboratory facilities exist, results are highly satisfactory (Norman 1957) However, such facilities are not universal, and an alternative approach seems desirable

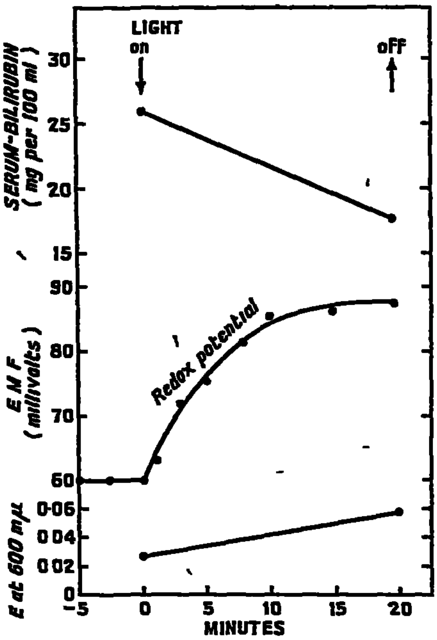

Fig 2—Effect of light on icteric serum.

Effect of Light on Serum-bilirubin

During serial estimations of the serum-bilirubin in jaundiced infants we noticed that their serum-bilirubin is highly photosensitive in vitro (Cremer, Perryman, Richards, and Holbrook 1957) We have studied this sensitivity and tried to apply it therapeutically

When icteric serum of infants is illuminated by white light, and the temperature is kept constant at 20°C, the characteristic 420 mμ absorption peak decreases and the absorption at the red end of the spectrum, around 550–650 mμ, increases a little (fig 1) At the same time the measured serum-bilirubin level is reduced and electromotive force (E M F) measurements show a positive increase in the oxidation/reduction (redox) potential of the system (fig 2) This indicates that, under the action of light bilirubin undergoes photo-oxidation or dehydrogenation to biliverdin or some intermediate products These substances are more polar, and therefore probably more easily excretable, than is bilirubin

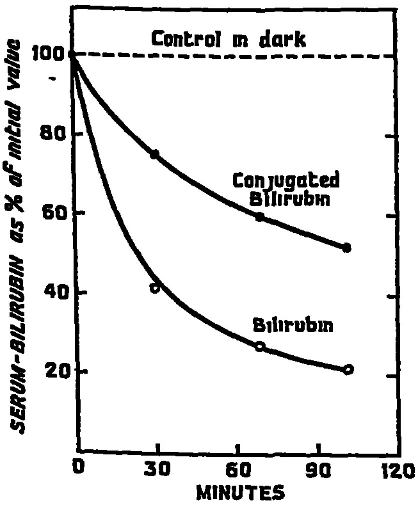

Fig 3—Effect of sunlight on serum-bilirubin.

Bilirubin (van den Bergh indirect pigment), the type of pigment greatly predominating in icteric infants, is some two or three times as photosensitive as is conjugated bilirubin (van den Bergh direct pigment) (fig 3)

These findings emphasise the need for special precaution in laboratories doing routine bilirubin estimations on jaundiced infants We now make a practice of enclosing all our blood-specimen tubes in light-tight containers if immediate analysis is not feasible We have found that specimens left in bright daylight may lose as much as 30% of their serum-bilirubin in an hour

Fig 4 shows the distribution of the photosensitivity effect over the visible spectrum

Clinical Applications

The subjects chosen for this study were all infants in the premature babies unit of the hospital The sister in charge of the unit had earlier reported the apparent fading away of the yellow pigmentation in the skin of jaundiced babies when they had been a short time in sunlight It was decided, therefore, to expose jaundiced infants to sunlight and assess the results quantitatively by serial determinations of serum-bilirubin

Before the exposure the general trend of the serum-bilirubin level was established by the micro-method devised for this purpose (Perryman, Richards, and Holbrook 1957) To avoid overheating or excessive ultraviolet radiation, the babies were placed naked in direct sunlight for fifteen to twenty minutes (according to the sun's intensity) and then withdrawn for similar periods before again being exposed to the sunlight. During the exposure the infants' eyes were protected by a simple plastic shield

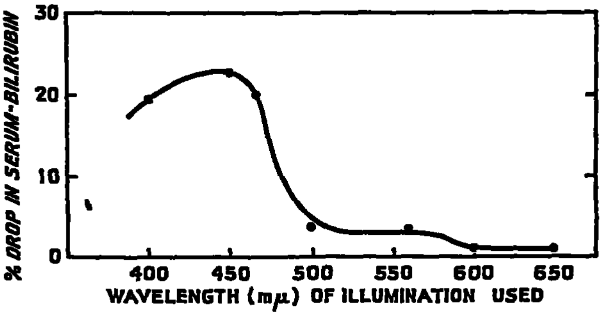

Fig 4—Spectral distribution of the photodestruction of serum-bilirubin

Jaundice quickly disappeared from the exposed areas of skin but persisted in areas which remained in the shade

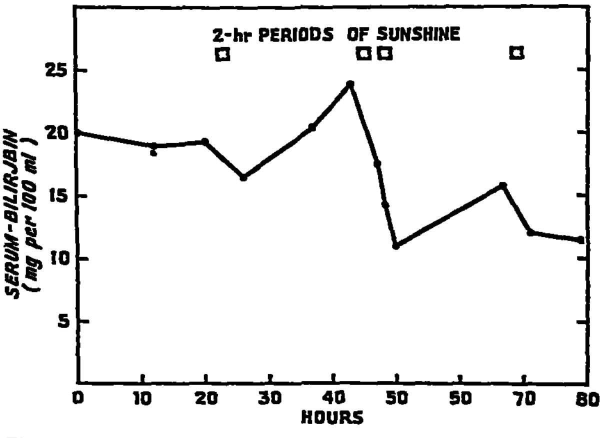

Fig 5—Sunshine treatment of an icteric infant with jaundice of prematurity (case 6)

TABLE I—EFFECT OF SUNLIGHT ON ICTERIC INFANTS

Case no	Birth weight (lb	oz)	Day of life	Serum-bilirubin before treatment (mg per 100 ml)	Duration of exposure (hours)	Resulting decrease in serum-bilirubin (mg per 100 ml)
1	5	2	6	25	2	4
2	5	2	5	24	3	6
			7	16	2	4
3	4	5	5	21	2	7
4	3	4	4	20	2	6
5	8	2	5	20	4	7
6	5	0	3	24	1	12
			4	19	2	2
			5	16	2	4
7	5	9	5	19	3	4
			6	15	2	2
8	4	5	2	18	3	2
			4	16	3	2
9	3	3	5	16	2	4
10	5	3	5	19	3	4
			6	15	3	2
11	3	12	5	12	2	3
12	5	14	3	11	2	4
13	5	3	4	10	2	—2
			5	12	2	0

After this intermittent sunlight treatment, bilirubin levels were again measured

Fig 5 shows a typical result of this treatment Table I records the initial level and drop in serum-bilirubin in 13 premature infants with twenty test exposures These had the so-called "physiological jaundice" of prematurity, and in all (except case 13, where there was a rise) there was a definite drop in serum-bilirubin during the exposure In general, we found that the higher the initial serum-bilirubin level and the longer the exposure-time, the greater the fall in serum-bilirubin

In view of these results, we sought a source of artificial light instead of sunshine Guided by our work on the spectral distribution of the photosensitivity (fig 4), we examined various light sources Finally the apparatus illustrated in fig 6 was devised

This consists of a hemicylindrical stainless-steel reflector suspended on a movable gantry and adjustable for height Eight 24 in light blue fluorescent 40-watt discharge tubes (G E C), at 2 in separation, are arranged around the curve of the reflector The equipment is so made that a cot may be wheeled beneath the lights, and switch-gear provides that the illumination can be cut if less than the full power is desired This equipment gives light of very high intensity in the region of 420–480 mμ without any dangerous ultraviolet or X-ray components The height of the lamp from the infant is adjusted to make use of the small amount of radiant heat emitted for keeping the infant's body-temperature at 98–100°F

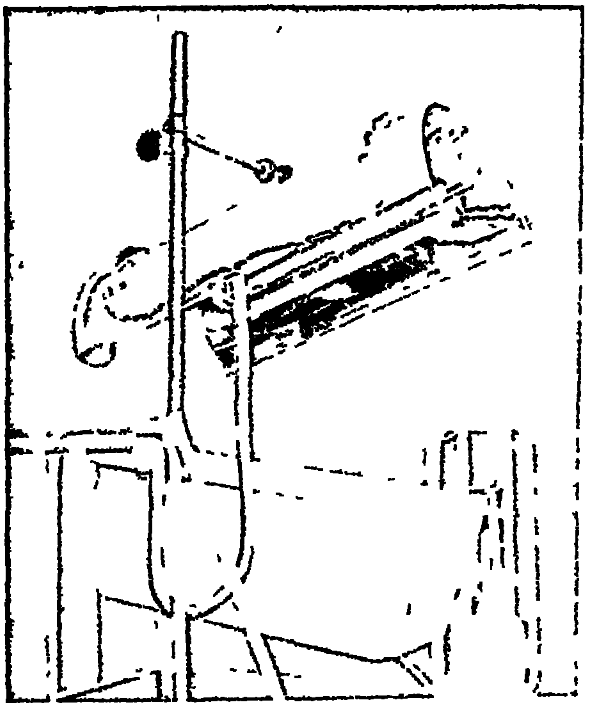

Fig 6—Artificial-light apparatus for cradle illumination of infants

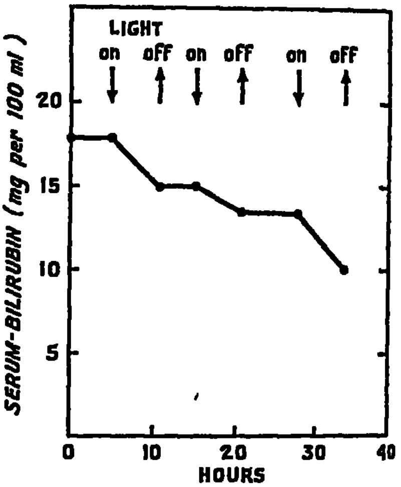

Fig 7—Effect of artificial-light treatment on a jaundiced premature infant (case 16)

Fig 7 shows the effect of this source of artificial light on an icteric premature infant, the coincidence of the drop in serum-bilirubin with the period of illumination is noteworthy

TABLE II summarises the results of twelve light-exposure tests in 9 jaundiced premature infants These all show small but significant drops in serum-bilirubin At first continuous illumination was used, but in the light of experience a routine of six hours in the lights followed by two hours out seems to give better results 2 infants with severe jaundice due to Rh incompatibility are not included in table II These failed to respond to the light treatment and exchange transfusion was necessary

TABLE II—EFFECT OF ARTIFICIAL LIGHT ON ICTERIC INFANTS

Case no	Birth weight (lb	oz)	Day of life	Serum-bilirubin before treatment (mg per 100 ml)	Duration of exposure (hours)	Resulting decrease in serum bilirubin (mg per 100 ml)
14	7	1	11	22	24	8
			12	14	20	3
			13	12	20	3
15	3	12	5	18	6	3
			6	14	6	3
16	4	12	5	19	36*	8
17	6	8	1	10	12*	5
18	6	14	1	13	24*	6
19	5	0	6	15	18*	6
20	5	3	8	14	18*	4
21	5	10	5	10	12*	2
22	6	7	4	12	24*	2

* Intermittent illumination 6 hours on, followed by 2 hours off

Discussion

Our results so far are insufficient for a complete statistical appraisal, but they encourage further work From our biochemical studies, it has become clear that a complex series of chemical changes is involved

Under the action of light, bilirubin seems to be dehydrogenated, and the role of hydrogen acceptors and photocatalysts is being investigated Several compounds accelerate the photodestruction of serum-bilirubin in vitro—e g, methylene-blue at a concentration of 10 μg per ml of serum, similarly toluidine-blue and cresyl-blue, though they are less effective, and riboflavine We suggest that the difference in degree of response to light treatment between one jaundiced infant and another and also the complete failure of some to respond may be related to lack of essential hydrogen acceptors or other factors in the circulating plasma We have found that in the first few days of life cœruloplasmin is absent from the blood-serum, which may have a bearing on this problem

No prospect can be entertained that this light treatment will prove a substitute for exchange transfusion in the erythroblastotic infant with active hæmolysis, but the method may be turned to clinical advantage in controlling the level of serum-bilirubin in cases of jaundice of prematurity

Summary

In some cases of neonatal jaundice the serum-bilirubin level is reduced by sunlight or by suitable artificial-light treatment

We should like to thank Dr R H Dobbs, consultant pædiatrician to this group, for his interest and encouragement, and Prof G H Lathe, of Leeds We are indebted to the group engineering department of the Southend Hospitals for the design and manufacture of the cradle illumination machine

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ACTION OF CITRATE AND OXALACETATE ON DIETARY AND DIABETIC KETOSIS

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THE effect of ketosis on the administration of Krebs-cycle metabolites has been extensively studied as a tentative approach to knowledge of this pathological condition It may be assumed, in fact, that ketosis develops whenever acetyl radicals are inadequately metabolised via the Krebs cycle, owing to a deficient availability of oxalacetate This pathogenic mechanism has also been postulated for diabetic ketosis (Thompson and King 1957), but Beatty and West (1955) did not detect any effect of the administration of succinic acid and malic acid on the ketonuria of alloxan-diabetic rats fed on Wesson oil, consequently they suggest that a deficiency of oxalacetic acid is not the cause of diabetic ketosis

To provide further evidence on this question the action of citrate and oxalacetate on experimental dietary and diabetic ketosis has been examined

Material

The rat and the dog were chosen for experimenting on because there is evidence that, in both species, the pathogenic mechanism of dietary ketosis (Crandall 1941, Deuel 1957) and alloxan-diabetic ketosis (Lukens 1948, Hoet and Young 1954) is essentially the same as in man However, because of the difficulty of obtaining stable ketosis of exclusively diabetic origin in the rat (Beatty and West 1955) and dietary ketosis in the dog (Crandall 1941) each type of ketosis was investigated in only one of these animal species Nevertheless a comparison between the results seems legitimate because, as mentioned above, the pathogenic mechanisms are essentially the same in the two species

TABLE I—EFFECT OF CITRIC ACID AND OXALACETIC ACID ON DIETARY KETOSIS

Treatment	No of experiments	Ketone bodies (mg per 100 g of body-weight in 24 hr)
Fasted 24 hr	8	1 0±0 5
Butyric acid	5	6 9±2 6
Butyric acid + 4 5 mM of oxalacetate	4	2 3±0 7
Butyric acid + 4 5 mM of citrate	4	1 6±0 7
Butyric acid + 6 0 mM of oxalacetate	4	0 6±0 3
Butyric acid + 6 0 mM of citrate	4	0 7±0 4

TABLE II—TYPICAL EXAMPLE OF EFFECT OF CITRATE AND OXALACETATE ON BLOOD-SUGAR AND KETONE-BODY LEVELS OF ALLOXAN-DIABETIC DOG FASTED FOR 6 HR

Administration of	Substance	Blood-level (mg per 100 ml)		
		Before administration	90 min after administration	180 min after administration
Citrate Na salt	Sugar	380 0	470 0	380 0
	Ketone bodies	16 7	16 5	15 0
Oxalacetate Na salt	Sugar	310	380 0	330 0
	Ketone bodies	25 3	23 3	22 3

Dietary ketosis was induced by feeding butyrate to female albino rats, the 24-hr urinary excretion of ketone bodies was determined by the method described by Greenberg and Lester (1944) with and without administration of citrate and oxalacetate (table I) A 10% solution of butyric acid adjusted to pH 6 0 was administered in the dose of 2 ml per 100 g of body-weight by stomach-tube to rats fasted 15 hr The millimols of the test substances injected intraperitoneously denote the dosage per kg of body-weight for 24 hr Oxalacetate was prepared according to the method described by Heidelberger (1953)

Experimental details and results are reported in table I

Diabetic ketosis was studied in alloxan-diabetic dogs, blood-sugar and ketone-bodies levels were determined before and after intravenous injection of citrate and oxalacetate (table II) Blood-sugar levels were determined by the method described by Somogyi (1945), and ketone bodies, expressed as acetone by that of Greenberg and Lester (1944) Citrate and oxalacetate were administered intravenously in a single dose of 3 mM per kg of body-weight The time intervals between the administration and the determinations were chosen on the basis of Crandall's (1941) results and are reported with other experimental details and data in table II

Results

The results show that dietary ketonuria is practically abolished by intraperitoneal injection of either citrate or oxalacetate

Diabetic ketosis, on the other hand, is not significantly influenced either by citrate or by oxalacetate injected intravenously

The discrepancy between the results obtained in diabetic and in dietary ketosis suggests that the pathogenic mechanisms responsible for these two conditions are fundamentally different

Diabetic ketosis may not be attributable, as dietary ketosis is, to a deficiency of oxalacetate or of citrate but rather, according to Beatty and West (1955), to a disturbance in the Krebs cycle

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REVERSAL OF URINARY DIURNAL RHYTHM FOLLOWING HEAD INJURY

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The presence of a diurnal rhythm of urinary excretion is well established (Vogel 1854, Quincke 1877, Simpson 1924, Norn 1929, Manchester 1933, Gerritzen 1940, Borst and de Vries 1950, Stanbury and Thomson 1950) Reversal of this rhythm has been reported in various conditions in which generalised œdema occurs—e g, congestive cardiac failure, malnutrition, cirrhosis of the liver, and the nephrotic syndrome (Quincke 1893, Sinclair 1949, Borst and de Vries 1950, Stanbury and Thomson 1951, Goldman 1951) The normal rhythm is also reversed in habitual night-workers (Norn 1929) and in some cases of Addison's disease (Levy et al 1946)

This paper describes a case in which reversal of the urinary diurnal rhythm followed a head injury The normal pattern of diurnal rhythm was also studied in five normal subjects under identical conditions

Material

Patient

A man, aged 40, was admitted to hospital under the care of Prof F T G Prunty in November, 1956, for investigation of progressive obesity accompanied by nocturia Apart from malaria and bacillary dysentery in 1936, he had been fit until July, 1945, when he was involved in a motor-cycle accident and was unconscious for several hours He had retrograde amnesia covering three days and post-traumatic amnesia covering seven days There was no external wound, but radiography revealed a fracture of the left parietal bone The patient was in hospital four months Electroencephalography before his discharge showed nothing abnormal In January, 1946, he began to have attacks of jacksonian epilepsy involving the left angle of his mouth, and in spite of phenobarbitone therapy he continued to have three or four mild attacks a year

RESULTS

—	Subject	Mean excretion (per 24 hr)	% of total daily excretion per 4 hr collection period *					
			From 8 P M to midnight	From midnight to 4 A M	From 4 A M to 8 A M	From 8 A M to noon	From noon to 4 P M	From 4 P M to 8 P M
Volume of urine	*Healthy volunteers*							
	No 1	1690 ml	13	7	6	19	35	20
	No 2	1761 „	14	8	7	28	29	14
	No 3	2377 „	11	8	4	12	35	30
	No 4	1509 „	23	10	9	15	22	21
	No 5	2389 „	12	8	6	18	34	22
	Patient	1883 „	19	25	21	12	12	11
Osmolality	*Healthy volunteers*							
	No 1	(m Osm /kg	935	1039	1095	825	649	774
	No 2	„	811	825	898	452	516	668
	No 3	„	749	693	897	690	330	320
	No 4	„	734	841	963	877	682	597
	No 5	„	747	782	867	601	372	501
	Patient	„	470	380	570	700	820	830
Total solutes	*Healthy volunteers*							
	No 1	1245 m Osm	16	12	8	20	27	17
	No 2	1620 „	20	11	10	19	26	14
	No 3	1545 „	17	12	10	12	27	22
	No 4	1655 „	22	12	9	18	21	18
	No 5	1940 „	18	10	10	19	23	20
	Patient	1073 „	16	17	20	14	17	16
Creatinine	*Healthy volunteers*							
	No 1	2629 mg	17	14	14	17	20	18
	No 2	2147 „	18	16	14	16	19	17
	No 3	2134 „	18	15	14	14	21	18
	No 4	2128 „	18	15	14	18	18	17
	No 5	2168 „	19	15	14	17	17	18
	Patient	1670 „	19	18	15	13	18	17
Sodium	*Healthy volunteers*							
	No 1	259 mEq	17	7	4	21	36	15
	No 2	243 „	20	9	6	21	29	15
	No 3	198 „	18	9	5	10	32	26
	No 4	218 „	27	13	5	15	22	18
	No 5	265 „	19	8	7	19	26	21
	Patient	201 „	19	18	21	14	15	13
Potassium	*Healthy volunteers*							
	No 1	98 mEq	17	10	10	25	27	11
	No 2	95 „	23	9	12	18	24	14
	No 3	77 „	16	8	11	17	32	16
	No 4	105	19	7	5	28	29	12
	No 5	89 „	13	5	9	29	34	10
	Patient	88 „	12	14	26	15	18	15
Phosphate	*Healthy volunteers*							
	No 1	1130 mg	23	23	16	6	14	18
	No 2	996 „	24	19	8	9	22	16
	No 3	973 „	20	25	11	14	10	20
	No 4	1069 „	21	24	17	10	11	17
	No 5	1061 „	22	14	10	9	19	26
	Patient	1047	18	14	14	8	24	22
Chloride	*Healthy volunteers*							
	No 1	295 mEq	15	6	6	23	35	15
	No 2	291 „	16	8	7	22	26	21
	No 3	224 „	14	6	7	14	35	21
	No 4	254 „	26	9	5	20	16	21
	No 5	284 „	17	5	7	22	30	19

* Values are percentages of mean total daily output except osmolality, which is mean of each period for three days

He denied any symptoms resembling narcolepsy and stated that his sleep pattern was normal Until 1945 his weight remained steady at about 64 kg, he then progressively gained weight, and on admission he weighed 118 kg He had not noticed any great increase in appetite, nor did he complain of excessive thirst. In 1952 he started to pass urine once or twice during the night and had done so ever since. He had no other urinary symptoms, and he stated that he did not drink large amounts of fluid in the evening or during the night.

On physical examination, apart from generalised obesity, nothing abnormal was found.

Investigation of renal function revealed no abnormality the specific gravity of the urine after deprivation of fluids was 1 028 and after the subcutaneous injection of vasopressin tannate 5 units it was 1·031. A twenty-four-hour creatinine clearance was 119 ml. per minute A glucose-tolerance test was normal The total daily urinary excretion of 17-ketosteroids and 17-ketogenic steroids and the response to corticotrophin were normal. A radiograph of the skull, a right carotid angiogram, and an electroencephalogram were within normal limits

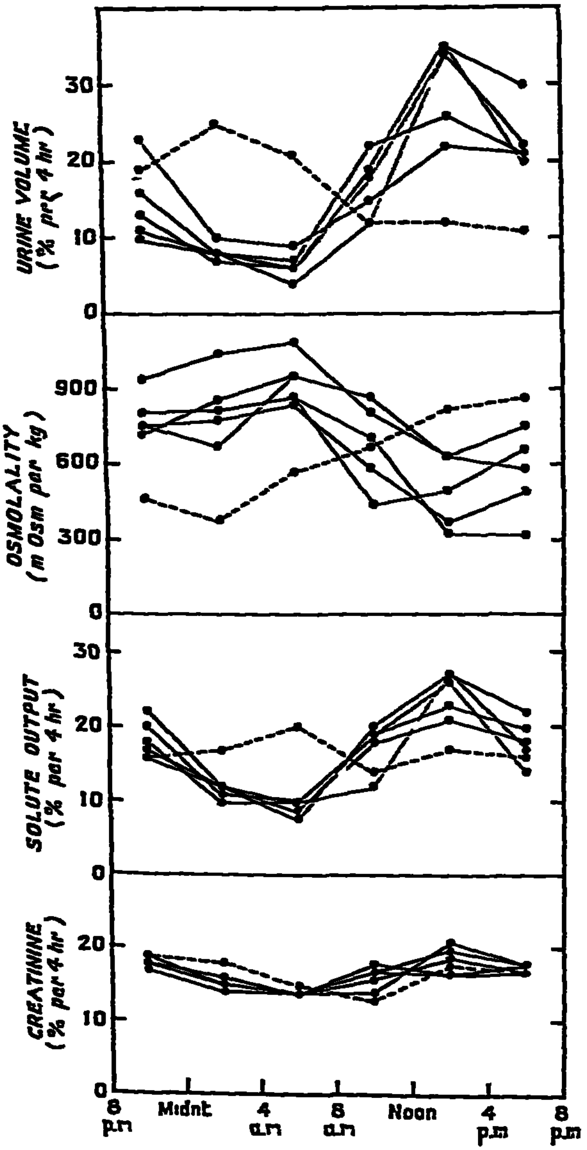

FIG 1—Diurnal changes in the flow and osmolality of the urine, and in total solute and creatinine excretion in normal subjects (continuous lines), and in the patient (interrupted lines). Values are percentages of mean total daily output except for the osmolality which is the mean for each period for three days.

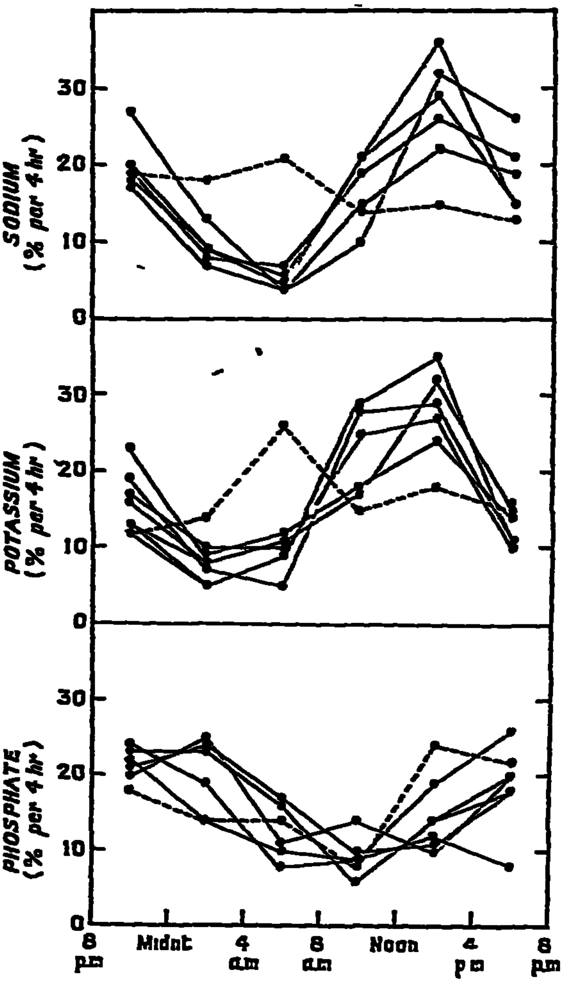

FIG 2—Diurnal changes in urinary excretion of sodium, potassium and phosphate in normal subjects (continuous lines) and patient (interrupted line).

Healthy Volunteers

Five healthy male volunteers were admitted to the metabolic ward for investigation.

Methods

During the three-day period of study both the patient and the normal subjects were ambulant by day but remained in the ward They were allowed to take as much food and fluids as they liked by day but nothing between 8 P.M and 6 A.M Urine was collected four-hourly from 8 P.M for seventy-two hours, eighteen specimens being obtained from each person. To distract attention from the volume of urine, and to reduce emotional influences on the flow of urine, the controls were told that the investigation concerned the pattern of urinary excretion of 17-ketosteroids and that this necessitated four-hourly collections of urine.

The volume of each specimen of urine was measured The osmolality of the urine was determined by measuring the depression of its freezing-point with a thermistor (de Wardener and del Greco 1955), the concentration of sodium and of potassium in the urine with a Barclay flame-photometer using an internal standard, creatinine by the method of Peters (1942), chloride by the method of van Slyke and Hiller (1947), and phosphate by Briggs' (1922) method. The 17-ketosteroids and 17-ketogenic steroids were determined by Dr R. V Brooks using the method of Norymberski (Gibson and Norymberski 1954)

The constituents of each of the eighteen specimens of urine from each person were determined by the above methods The mean outputs of the six corresponding four-

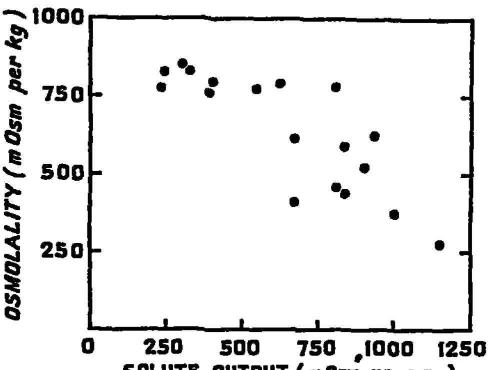

Fig. 3—Osmolality and excretion of solutes in all four-hour specimens of urine obtained from normal subject no. 5.

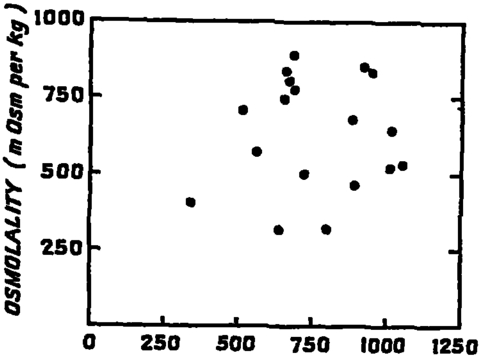

Fig. 4—Osmolality and excretion of solutes in all four-hour specimens of urine obtained from the patient.

hour periods each day were calculated, and from this the mean total daily output was determined. The mean output of each four-hourly period has been expressed as a percentage of the mean total daily output.

Results

The results are given in the accompanying table.

Normal Subjects

The normal subjects showed little day-to-day change in their pattern of urinary excretion, and the patterns were similar in all of them. The highest and lowest rates of excretion mentioned below represent the mean of all five subjects during any one four-hour period.

The output of water, total solutes, sodium, potassium, chloride, and creatinine increased during the day being greatest from noon to 4 P.M., and at this time the urine was most dilute. Conversely, the excretion of these same substances decreased during the night, being least from 4 A.M. to 8 A.M., except for potassium which was usually lowest in the previous period—i.e., from midnight to 4 A.M. The urine was most concentrated from 4 A.M. to 8 A.M. (figs 1 and 2).

The excretion of water, sodium, potassium, and chloride showed the greatest diurnal changes, their highest excretion-rate was usually at least four times their lowest. Changes in the output of total solutes were less marked, the highest excretion-rate being less than three times the lowest. The excretion of creatinine fluctuated even less, the highest excretion-rate being 1.4 times the lowest. There was an inverse relationship between the total output of solutes and the osmolality of the urine (fig 3).

The rhythm of the urinary excretion of phosphate was the reverse of the other substances studied and was more variable both from one person to another and from day to day. The highest excretion-rate was from 8 P.M. to midnight and the lowest from 8 A.M. to noon (fig 2).

Four-hour excretion-rates of 17-ketosteroids and 17-ketogenic steroids were variable but were lowest by night and highest in the forenoon; in some subjects they rose again in the evening. Changes in the excretion-rates of these steroids seemed to be unrelated to changes in the excretion-rates of the other constituents of the urine.

Patient

In the patient the diurnal rhythms of urinary excretion of all the substances studied differed from those found in the normal subjects, but were consistent from day to day.

The output of water, total solutes, sodium, potassium, and creatinine increased during the night. The highest excretion-rate of water was from midnight to 4 A.M. and preceded the highest excretion-rate of total solutes, sodium, and potassium by four hours. The urine was most dilute during the period of highest water excretion.

Throughout the day the output of water, total solutes, sodium, and potassium was less than during the night, and there was little difference between the three periods. The concentration increased during the day and was greatest from 4 P.M. to 8 P.M. The pattern of excretion of creatinine was similar to that in the normal subjects, but the lowest excretion-rate was four hours later, from 8 A.M. to noon; it was unrelated to changes in the output of total solutes (fig 1).

As in the normal subjects, the excretion of water, sodium, and potassium showed the greatest diurnal changes, but they were less pronounced. The highest excretion-rates of water and potassium were about twice, and those of sodium and total solutes only 1.5 times the lowest. There was no relationship between the output of total solutes and the osmolality of the urine (fig 4).

The pattern of urinary excretion of phosphate resembled that in the normal subjects, but both the lowest (8 A.M.–noon) and the highest (noon–4 P.M.) rates occurred by day and in consecutive periods (fig 2).

The urinary excretion of 17-ketosteroids and 17-ketogenic steroids was variable, as in the normal subjects, but appeared to show a normal diurnal rhythm.

Discussion

In the normal subjects, the diurnal patterns of urinary excretion of water, sodium, potassium, chloride, and creatinine were similar to those observed by other workers (Simpson 1924, 1926, Norn 1929, Manchester 1933, Gerritzen 1940, Smits 1947, Borst and de Vries 1950, Stanbury and Thomson 1950, Goldman 1951). It was also confirmed that the urinary excretion of phosphate varies considerably more than that of water and strong electrolytes. The excretion of water and total solutes decreased during the night, whereas the osmolality of the urine increased. In contrast, during the day the excretion of water and total solutes increased, and the osmolality of the urine decreased. There was an inverse relationship between the output of solutes and the osmolality of the urine, and the rhythms of excretion of water and osmolality total solutes were synchronous.

In the patient the most striking feature was a reversal of the normal pattern of excretion of water, more water being excreted by night than by day. There was also a reversal of the diurnal rhythm of urinary excretion of total solutes, sodium, and potassium, and some change in the excretion of phosphate and creatinine. There was no relationship between the output of solutes and the osmolality of the urine, and the rhythms of excretion of water and total solutes were not synchronous.

The rate of flow of the urine is determined by (1) the concentration of antidiuretic hormone (A.D.H.) in the plasma (Verney 1946), (2) the tubules' capacity to respond to A.D.H. (Epstein et al. 1957, de Wardener and

Herxheimer 1957), and (3) the rate of solute output (McCance 1945, de Wardener and del Greco 1955) The nocturia in this patient appears to have been induced by a change in at least two of these mechanisms Unless large amounts of vasopressin are administered, it is impossible to differentiate between (1) and (2), but one of these two mechanisms must have been responsible for the evening rise in urine flow and fall in urine concentration (from 830 to 470 m Osm kg of the urine in the periods 4 P M - 8 P M. and 8 P M -midnight, because the output of solutes in these two periods was identical Nevertheless in the following period (from midnight to 4 A M) the high rate of urine flow was maintained, at least in part, by an increased output of total solutes This occurred at a time when the initial cause of the nocturnal diuresis was waning, for as the solute output rose the urine became more concentrated It is therefore concluded that the increased excretion of water at night in the patient was due to a nocturnal increase in the output of solutes, and in addition to at least one of the two mechanisms which are independent of the output of solutes

It is probable that in normal subjects the diurnal variation in water excretion is also controlled by factors other than the solute output, though this is not apparent under normal conditions Lewis and Lobban (1956), for instance, have shown that the diurnal rhythm of urinary excretion of water and that of electrolytes can become dissociated in certain circumstances In addition, Lewis and Lobban (1956) and Mills and Thomas (1957) have shown that the diurnal excretion of individual electrolytes may vary independently These findings suggest that the mechanisms responsible for the diurnal rhythms of the urinary excretion of water and of individual electrolytes are independent

In the present patient a reversal and dissociation of the normal urinary diurnal rhythms of water and electrolyte secretion followed a head injury, and was associated with the onset of epilepsy and obesity This suggests that the site of the control of the various mechanisms responsible for the diurnal rhythms of urinary excretion is in the brain, possibly in the hypothalamus—a suggestion previously advanced by Mills (1951) and by Lewis et al (1956) from their experiments on normal subjects

Summary and Conclusions

A case is reported in which reversal of the urinary diurnal rhythm, epilepsy, and obesity followed a head injury

The daily patterns of urinary excretion of water, total solutes, sodium, potassium, chloride, phosphate, and creatinine and of urine osmolality were studied in five normal subjects and compared with those in the patient

The high rate of excretion of water at night in the patient appears to have been due to an increase in solute output, and to a mechanism independent of the solute output

It is suggested that the mechanisms responsible for the diurnal rhythms of urinary excretion of water and electrolytes are independent.

It is further suggested that the site of control of these mechanisms is in the brain, possibly in the hypothalamus

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EXTENT OF THE INFARCT IN THE ANTERIOR LOBE OF THE HUMAN PITUITARY GLAND AFTER STALK SECTION

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A QUESTION of considerable importance, both to neurosurgeons and to those interested in the treatment of cancer, is the efficiency, or otherwise, of section of the pituitary stalk as a means of producing necrosis of the anterior lobe of the gland Although stalk section is simpler than total hypophysectomy, its efficacy is not yet proved

The following case shows the extent of the lesion produced

Case-report

A woman, aged 39, had had a left radical mastectomy performed by Mr J Heriot of King's College Hospital in July, 1956 She remained well till March, 1957, when she was found to have a left pleural effusion. She was given methyl testosterone and in July was admitted to the Guy's-Maudsley neurosurgical unit (no 1767) She now had metastases on the left lower chest wall, the left pleural cavity was virtually obliterated by growth, and there were metastases in bones

At the urgent request of the patient and her relatives, an operation was performed on Aug 9 (P H S) A frontal osteoplastic flap was turned and the right frontal lobe was raised to expose the pituitary stalk. This was cut and a plate of cold-curing resin,† shaped to fit beneath the optic chiasma and over the diaphragma sellæ, was inserted to separate the cut ends of the stalk and thus prevent any possible regrowth of vascular connections (fig 1) (Harris 1950, Harris and Jacobsohn 1952, Jacobsohn 1954)

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* Assisted by a grant from the Bethlem Royal and Maudsley Hospital Research Fund

† Simplex pentacryl', Dental Fillings, Ltd , 49, Grayling Road, London, N 16

Eight days later the patient developed congestive cardiac failure and pericarditis She died on Aug 28

Necropsy (P M D)

There were multiple secondary deposits of carcinoma, and severe bronchopneumonia The brain showed minimal operative trauma and contained no secondary deposits The plastic plate (fig 1) lay in excellent position over the diaphragma sellæ. At the proximal cut end of the pituitary stalk was a little rounded knob resembling a tiny neuroma on a peripheral nerve—an appearance which we have commonly seen after hypophysectomy

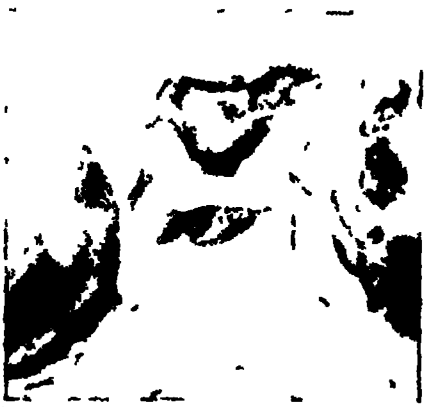

Fig 1—Photograph, taken at necropsy, after removal of the brain, showing the plastic plate in situ, lying beneath the optic chiasma

Findings in the Pituitary Gland

The gland was fixed in formol-saline and cut sagittally into five blocks and embedded in paraffin wax Sections were taken from one surface of each block and stained with hæmatoxylin and eosin, iron hæmatoxylin and van Gieson's mixture, Mallory's trichrome method, Heidenhain's azan method, Mann's method, and the periodic-acid Schiff method

The sections showed extensive infarction of the anterior lobe There was a narrow rim of living cells all round the periphery, but deep to this, in the lateral portions, the epithelial tissue was wholly necrotic (fig 2) In the median part of the gland the infarct was confined to the anterior (ventral) half of the anterior lobe, and the cells in the posterior (dorsal) half were alive (fig 3) The situation and the extent of the living and necrotic tissue is shown in fig 4, which is a reconstruction based on sections taken from the five blocks

Fig 2—Sagittal section through the lateral part of the pituitary Only anterior-lobe tissue is present Note the massive infarct (pale) and the narrow peripheral rim of surviving anterior-lobe cells (dark) (hæmatoxylin and eosin ×9)

From the infarct the epithelial cells had completely disappeared the whole of its central area was occupied by structureless debris with no nuclear remains Round the periphery of this structureless mass there was a layer of young granulation tissue The boundary between the granulation tissue and the living cells was sharply defined No inflammatory cells were present around the infarct In the living anterior-lobe tissue, the sinusoids were dilated and filled with red cells, and the tissue in general appeared œdematous, the epithelial cells, though alive, appeared distinctly abnormal They were, on the whole, unusually small, had lost their regular arrangement, and tended to be heaped together in irregular, closely packed groups Many cells had a glassy acidophilic cytoplasm, and few showed any distinct intracytoplasmic granules

The posterior (neural) lobe was invaded by carcinoma cells, which is not unusual in mammary carcinoma In this case the lobe was probably invaded before the stalk was cut The neural tissue itself was shrunken and fibrotic, there was also an apparent increase in the cellularity of this tissue and in the number of blood-vessels These latter appearances were similar to those seen in the posterior lobe of goats 3–4 weeks after pituitary-stalk section (Daniel and Prichard 1958)

Comment

The large extent of the infarct in the anterior lobe in this case is evidence that most of the anterior lobe derives its blood-supply from the long hypophysial portal vessels of the pituitary stalk, which were severed at operation The posteromedian area of the anterior lobe survived because this area is supplied by the short hypophysial portal vessels, which have their origin in the lower infundibular stem (fig 5), and thus is supplied by the intact inferior hypophysial arteries

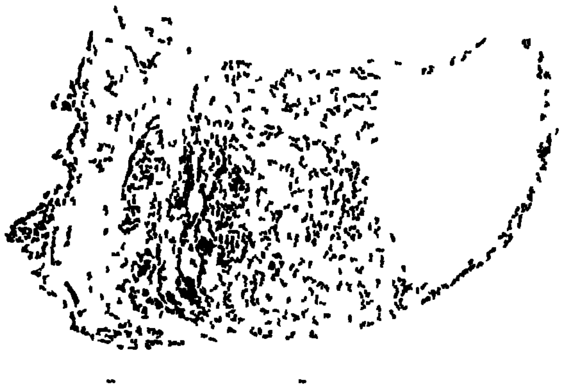

Fig 3—Approximately mid-sagittal section through the pituitary Posterior lobe (somewhat fragmented and with carcinoma tissue in it) seen on the left In this plane there is an area of surviving anterior-lobe tissue (dark) occupying the posterior half of the anterior lobe, but this area was confined to a median zone (see fig 4) On the right the anterior lobe is infarcted (pale area) (hæmatoxylin and eosin ×7½)

The anterior lobe of the human pituitary has no direct arterial blood-supply (Xuereb, Prichard and Daniel 1954a) This is also the case in some animals (but *not* the rabbit), and a comparable picture of massive infarction of the anterior lobe is regularly seen in sheep, goats, and rats after pituitary-stalk section or cauterisation of the hypophysial portal vessels in the pituitary stalk (Daniel and Prichard 1956, 1957a, 1957b, 1957c, 1958) These animals, like our patient, have a small area of surviving anterior-lobe tissue, which does not derive its blood-supply from the stalk and also a narrow peripheral rim of surviving anterior-lobe cells, whose survival we attribute to the diffusion of oxygen and metabolites from the adjacent, highly vascular, dura mater

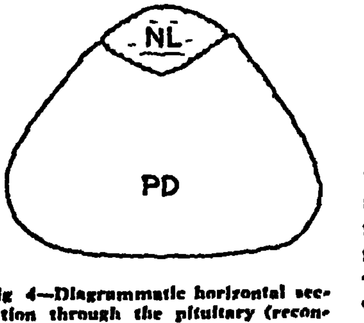

Fig 4—Diagrammatic horizontal section through the pituitary (reconstructed from sections) showing extent of the infarct (pale) and the surviving tissue (dark) in the anterior lobe (P D) N L, neural (posterior) lobe

Fig 3 alone is misleading as to the extent of the *infarct* The

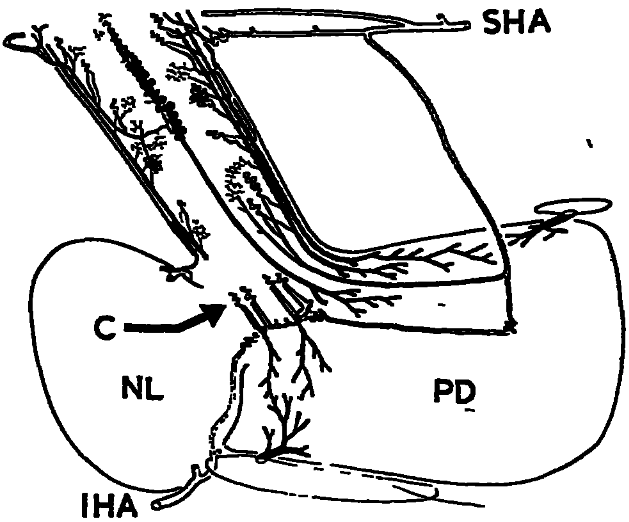

Fig 5—Diagram showing the blood-supply of the anterior lobe (P D) of the human pituitary, in sagittal section

Section through the pituitary stalk does not interfere with the blood-supply to the capillary loops (C) in the lower infundibular stem It is the blood-flow through the short portal vessels draining these capillary loops which has kept alive the posteromedian area shown in figs 3 and 4

N L, neural (posterior) lobe, S H A, superior hypophysial artery, I H A, inferior hypophysial artery (This diagram is modified from fig 16, Xuereb et al 1954b, and further explanations will be found in that paper)

large mass of living epithelial cells seen here is, in fact, confined to a narrow median strip, and sections from the more lateral blocks (fig 2) show that much the greater part of the lobe is necrotic (fig 4) To see the extent of the necrosis at a glance it would be wise to cut the pituitary horizontally, as was done by Russell (1956), who demonstrated very similar appearances

Our patient survived for 3 weeks after operation In goats (Daniel and Prichard 1958), results were very similar to those reported here, and there was a suggestion of some regeneration of anterior lobe cells after a few days

In the goats, as in our patient, the abnormal appearance of the epithelial cells surviving in the anterior lobe was very striking This appearance, we believe, indicates that the living cells had lost much of their functional activity as a result of the stalk section, because the remaining part of the primary capillary bed (in the lower infundibular stem) had been "denervated" by section of the pituitary stalk The neural component of the neurovascular link between the hypothalamus and the anterior lobe, which Green and Harris (1947) and Harris (1955a, 1955b) consider essential for the proper maintenance of anterior-lobe function, was now missing

The degeneration of the neural tissue in the posterior lobe was not, we think, primarily due to carcinomatous infiltration, since the same picture was seen in the posterior lobes of the goats 3–4 weeks after stalk section, and is only to be expected after section of the nerve tracts

Summary and Conclusions

In a woman with carcinomatosis, section of the pituitary stalk led to infarction of the anterior lobe except for the posterior half of the median part and a few cells round the periphery (The full extent of the necrosis in the anterior lobe after section of the pituitary stalk is not revealed by median sagittal sections)

Section of the pituitary stalk in man will not cause necrosis of the entire anterior lobe of the pituitary gland But even in "total" hypophysectomy fragments of this lobe are almost always left behind in the sella turcica, and this residual tissue may be found in patients with a successful remission of the malignant growth Moreover, all reports of extensive infarction of the anterior lobe in man mention a narrow peripheral layer of surviving anterior-lobe cells However, from experimental work on animals, it seems probable that any surviving cells, when isolated from the hypothalamus either by pituitary stalk section or by subtotal hypophysectomy, have their secretory activity so much reduced that they are no longer endocrinologically important Histologically they are abnormal in appearance

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GANGRENE OF THE EXTREMITIES FOLLOWING CARDIAC INFARCTION AND NORADRENALINE THERAPY

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M B Lond , M.R C.P
MEDICAL REGISTRAR, LONDON HOSPITAL, E 1

Symmetrical peripheral gangrene is a rare complication of heart-disease with circulatory failure The following case is of interest in that the gangrene was of unusual extent and the patient had been treated with noradrenaline

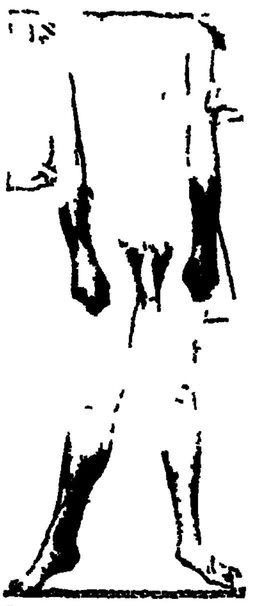
Case-report

A man, aged 56, was admitted to the London Hospital on Aug 18, 1957, having collapsed three hours before with severe lower substernal pain There was no previous history of significant ill health

On examination his extremities were cold and blue, his skin was pale and clammy, and his temperature was 95 5°F His pulse was feeble, rhythm regular, rate 40, and apex-beat impalpable, and the heart sounds were distant, with gallop rhythm There was no jugular venous distension, and no crepitations were heard at the lung bases The blood-pressure was 80/50 mm Hg Electrocardiography showed gross ST and T changes in all leads and complete heart-block

Treatment and course —Morphine and anticoagulants were given, the latter being discontinued after a vomit of about a pint of blood twelve hours later Four hours after admission there was no change in the patient's general condition and blood-pressure and an intravenous infusion of noradrenaline 1 200,000 in 5% glucose was begun The concentration was increased to 1 100,000 after about an hour to reduce the amount of intravenous fluid given The blood-pressure rose almost immediately and was maintained at about 110 mm Hg systolic and 70 mm Hg diastolic The pulse-rate rose to 80, and electrocardiography showed that sinus rhythm had returned There was also concurrent improvement in the patient's general condition The infusion was maintained for sixty-eight hours, after which the blood-pressure spontaneously remained normal 20 mg of noradrenaline was given on the first day, 16 mg on the second day, and 8 mg on the third, the rate of infusion being adjusted according to the blood-pressure.

Ordinary transfusion needles were used and the site of infusion was changed twice—at points just above the wrist in both arms, and above the internal malleolus in the right leg Towards the end of the third day the peripheral pulses became difficult to feel On the fourth day the patient complained of stiffness of the fingers of his left hand, and during the next two days patches of gangrene appeared on his hands and feet Thereafter gangrene spread gradually up all four limbs to the extent shown in the accompanying figure No urine was passed during the first thirty-six hours Measurements were not made after that, because of incontinence, but the flow appeared to be adequate, and a catheter specimen had a specific gravity of 1 025 The patient became delirious and progressively weaker and developed moderate engorgement of his jugular veins and a few crepitations at his lung bases He died fourteen days after admission The hæmoglobin on the fifth day was 70%, and the blood-urea on the day of death 212 mg per 100 ml



Gangrene of all four limbs

Necropsy revealed extensive cardiac infarction The whole of the posterior wall of the right ventricle, the posterior two-thirds of the interventricular septum, and the whole of the posterior wall of the left ventricle were necrotic The left coronary artery, which rose from the right aortic sinus and wound round the aorta, was much smaller than usual, most of the blood-supply to the heart coming from the right coronary artery, which was occluded 2 cm from its origin by a thrombus 4 5 cm long surrounded by a crescent of atheroma There was moderate atheroma throughout the aorta, and there were a few streaks in the carotid and femoral arteries The limb arteries were shown either by dissection or injection radiography to be patent and apparently free from thrombus as far as the line of demarcation of the gangrene There were a few petechial hæmorrhages in the stomach, the liver and the spleen were congested, and the kidneys appeared normal both to the naked eye and on microscope There was moderate pulmonary œdema, and a few ante-mortem thrombi were found in some of the smaller pulmonary arteries Apart from the limbs, the testes were the only organs to show ischæmic necrosis

Discussion

Fishberg (1938) observed that, in heart-failure, the antecubital veins might be collapsed when the jugular veins were distended, and he postulated selective vasoconstriction conserving the circulation for vital organs Freis et al (1952) considered that peripheral vasoconstriction in cardiac infarction was a reflex mechanism produced by a reduction in the stroke-volume of the heart Gangrene of the extremities may be considered to be an unfortunate effect of this compensatory mechanism

During the past twenty years several reports of this complication have appeared Perry and Davie (1939) observed it in hypertensive heart-failure, Abrahams (1948), reported incipient gangrene in paroxysmal tachycardia, and Swan and Henderson (1951), Schulz and Knobloch (1953), Bird et al (1954), and Caserta et al (1956) describe it in cardiac infarction

In the present case the use of noradrenaline must have made an important contribution to the vasoconstriction that led to gangrene The spread of the gangrene for eleven days after the infusion had been stopped indicates the equal or greater importance of the low cardiac output These two factors may explain the remarkable extent of the gangrene In the other published cases it usually involved little more than the tip of the nose and the digits

Although local necrosis at or near the site of infusion is not uncommon, I have not been able to find a published report of symmetrical peripheral gangrene after the use of noradrenaline The doses of noradrenaline given in the present case were fairly large, but larger doses have been given in similar circumstances by various workers—e g, Smith and Guz (1953)—without ill effect Caserta et al (1956) used mephentermine sulphate, another powerful peripheral vasoconstrictor, but there was a clear interval between stopping the drug and the development of gangrene Humphreys et al (1955) described several cases of skin gangrene following noradrenaline therapy, but these all appeared to be due to local leakage of the drug into the tissues This mechanism was not important in the present case, because the left leg, which received no infusion, became gangrenous like the other limbs

I must thank Dr R R Bomford and Prof D S Russell for permission to publish

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INSTRUMENT TO AID VOICE-TRAINING OF PROFOUNDLY DEAF CHILDREN

G R G PLANT
M C, M A Cantab

THE wearing of hearing-aids is of great help to partially deaf children, and the introduction of auditory training with powerful group hearing-aids in the children's classrooms has proved to be of benefit to children with very limited hearing, but the deafness of many grade-III pupils at schools for the deaf is so profound that they can derive little benefit from auditory equipment, even of the most powerful kind, and for these children reliance continues to be placed on speech-training methods which accept the fact that they are unable to hear either their own voices or those of their teachers

In such training a profoundly deaf child can be taught how to coordinate the various parts of his mouth and throat so as to produce the different types of vowel and consonant sounds which make up speech, and in time he will learn how to put the sounds into order to form words and sentences However, an aspect of speech which he cannot understand is the variation in frequency, or "pitch", that people with normal hearing impart to their voices during conversation This upward and downward variation in the fundamental frequency of the vocal cords, known as "voice inflexion", is used extensively in ordinary speech to convey intelligibility and meaning, and experiments show that a frequency variation of almost an octave is often used Because there is no satisfactory way of teaching a profoundly deaf child how to vary the pitch of his voice, everything that he says tends to be delivered on one constant monotone or with faulty voice inflexions Thus, however clearly he may have learnt to enunciate his words, ordinary people find his speech peculiar and difficult to understand

Previous Apparatus

In an endeavour to meet this situation various forms of visual pitch-indicating apparatus have been devised during the past quarter of a century, but, so far as is known, none of the apparatus has yet been considered to be sufficiently simple or robust for it to be manufactured and brought into general use for children at schools for the deaf

Frahm (1901) described an electromagnetically operated bank of spring reeds for indicating varying frequency

Hunt (1935) described a direct-reading frequency meter using two thyratrons, and suggested that it would help the deaf

Walton (1936) described an optical recording and frequency-indicating apparatus for analysing sound-waves magnetic circuits being used in parallel

Obata and Kobayashi (1937) described a direct-reading pitch recorder for indicating the fundamental pitch level in music and speech

Coyne (1938) described a voice-pitch indicator having a series of tuning forks, each operating a lamp

Sterne and Zimmermann (1939) described a voice-inflexion indicator in which seven lamps were arranged to be lit by thyratrons the number of lamps alight at any time varying in accordance with the fundamental frequency of the applied wave.

Horwitch (1948) described inflexion apparatus for the speech training of deaf persons, using eight reed filter circuits

Jones (1956) described a tonometer for linguists and deaf persons, using a bank of electromagnetically operated spring reeds

Present Apparatus

Some experiments which I started a few years ago have now led to the development of a new voice-training instrument, whose principal purpose is to demonstrate to a deaf child the pitch of his voice while he is speaking

The overall size of the first prototype instrument is 9 inches×9 inches×14 inches, and it is believed that there will not be any difficulty in manufacturing it. Much assistance has been afforded to me in the final stages of development of the prototype by Miss E M Johnson, headmistress of the Old Kent Road School for the Deaf, London, and preliminary trials being conducted at the school with profoundly deaf children are showing considerable promise

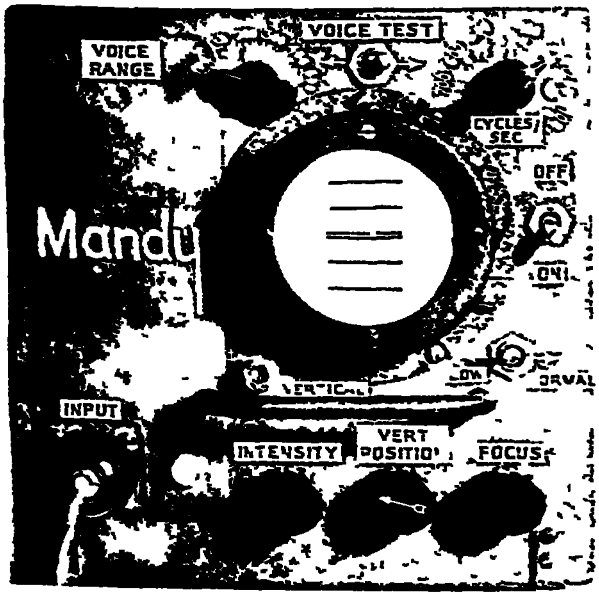

Fig 1—Front panel of voice trainer

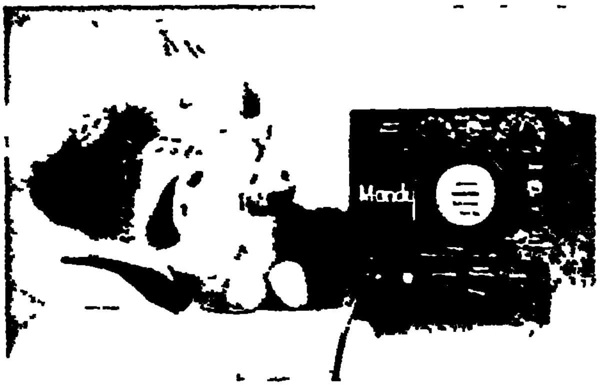

Fig 2—Child viewing voice trainer note collar bearing microphone on child s neck.

The front panel of the prototype instrument is shown in fig 1 and in fig 2 a child can be seen viewing the screen of the instrument in readiness for a voice-training exercise

The operation of the instrument is such that the effect of any extraneous noise is suppressed and the complex sound-wave generated by the child's voice is analysed so that only the fundamental frequency of the vocal cords is presented as a visual signal The child sees the pitch of his voice as a beam of light moving up and down the screen with the upward and downward variation of frequency, the beam disappearing when there is no vocal-cord vibration The controls of the instrument are set so that the chosen mean frequency above and below which the child is to vary his voice, appears on the central horizontal line on the screen, and the trials indicate that the frequency range demonstrated between the highest and lowest lines on the screen should be set at about an octave In fig 1 the instrument shows a mean frequency of 300 cycles a second, and in fig 2 a frequency of 400 cycles a second has caused the beam of light to move up the screen to a position between the two upper lines The prototype has been designed so that any part of the range of the human voice may be chosen, and it is therefore possible for men and women as well as children with high-pitched voices to use the instrument

So that the necessary funds may be raised to meet the costs of further tests and development before the final form of the instrument is determined for manufacture. a non-profit-making association, Speech Research for the Deaf, Ltd , has been incorporated, whose registered office is at 116–118, Chancery Lane, London, W C.2 The instrument is the subject of British patent application no 5569 57, and all rights for the invention have been assigned to Speech Research for the Deaf, Ltd Further forms of research will be undertaken as soon as the financial resources of the association reach a point where this is possible

I wish to thank Dr T S Littler, director, Wernher Research Unit on Deafness. for help and encouragement since the first prototype instrument was demonstrated to him last year

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Medical Societies

ROYAL SOCIETY OF MEDICINE

Tetanus

THE Section of Experimental Medicine and Therapeutics and the Section of Neurology met jointly on May 13 with Prof J V DACIE in the chair

Prof G PAYLING WRIGHT reviewed the use of anti-tetanus serum (A T S) since its discovery by von Behring in 1890 In therapy, the antitoxin was soon found to be disappointing, but its value in prophylaxis was promptly recognised in veterinary surgery For man, it first showed its value on a mass scale by the striking fall in the incidence of tetanus which followed its general issue as a prophylactic agent among the wounded in the 1914–18 war

More recent studies on the persistence of injected A T S in children had shown that doses of 100,000 units (as used by Cooke et al 1943) probably maintained a protective level for six weeks, but the usual prophylactic dose of 1500 units (Bigler and Werner 1941) probably became ineffective after half that time

The hazards of anaphylactic reactions to a second injection of horse serum were well known, but the danger of "*tetanus post-serique*", which might result from prior sensitisation to horse-serum antitoxin and its consequent accelerated removal from the blood, was not sufficiently appreciated In studies on animals, Professor Wormall, of St Bartholomew's Hospital, had contrasted, with the aid of isotopic labels, the rates of loss of horse-serum gamma-globulin in normal and in previously specifically sensitised rabbits In the latter, a very large loss occurred even in the first ten minutes after fifty minutes only about a tenth was still in circulation Laws and Payling Wright had made similar experiments in 1952, using purified labelled bovine proteins in the previously immunised animals, little of the protein remained in the blood after twenty-four hours Laws later showed not only that these proteins were more rapidly removed from circulation but that they were also more quickly destroyed, because labelled polypeptides and other degradation products appeared more promptly in the urine

A probable instance of a failure of prophylaxis in consequence of previous "immunological education" to horse serum-proteins was the case of "*tetanus post-serique*" reported by Littlewood, Mant, and Payling Wright in 1954 A 14-year-old boy injured himself with an exploding home-made bomb and was given surgical and antibiotic treatment together with 1500 units of A T S Six months later, he again injured himself through another, almost identical, explosion and again received treatment together with 1500 units of A T S Twelve days later he developed trismus A trial dose of 0 1 ml A T S produced a general reaction, but eventually 100,000 units was given Despite treatment he died seventeen days after the injury The authors concluded that the prophylactic dose of A T S on the second occasion had been ineffective through its accelerated destruction They made two important recommendations first, that once A T S has been given to a patient, he should after a lapse of a few weeks be immunised actively with diphtheria and tetanus toxoid and second, that before any reconstructive surgery is carried out in a potentially tetanus-spore-infected area, a course of active immunisation should be given

Dr D R LAURENCE made the point that there was no general agreement on which drug was the most effective anticonvulsant, and this resulted in the polypharmacy with drugs of unknown potency commonly used in treating tetanus The ideal drug was one which abolished the convulsions but which did not interfere with respiration or seriously impair consciousness It was justifiable to use animals for testing the effectiveness of drugs because it had been shown that animals and man responded similarly to tetanus Local hind-limb tetanus was produced in rabbits by the injection of a small quantity of tetanus toxin, and electromyograms were recorded after a standard afferent stimulus in the form of an electrically operated tap to the frame supporting the animal The electrical responses from the muscles so obtained were electronically integrated and converted to arbitary units which were automatically counted Using this quantitative response it was possible to obtain accurate comparative bioassays of the anti-tetanus activity of many drugs It was found that the phenothiazine derivatives were much more potent than mephenesin Acetylpromazine was by far the most potent drug yet tested and it gave an activity ratio of 10 5, compared with chlorpromazine 1 0, promazine 0 46, and promethazine 0 32

A Bantu woman with local tetanus in her legs allowed similar studies to be made in a human subject using the stretch reflex as the stimulus It was shown that chlorpromazine and thiopentone both abolished the tetanus response, but even after thiopentone "emotional conversation" caused a return of the response but "sedative conversation" abolished the response This emphasised the fact that in the presence of fear and pain higher doses of drugs were needed to control convulsions

Although chlorpromazine had been used in anæsthetic practice since 1950, its selective anti-tetanic effects had probably been overlooked owing to underdosage and to the fact that it was never used alone Following the demonstration of its powerful anti-tetanic effect in animals Dr R E Kelly and Dr Laurence controlled severe tetanus spasms in a boy of $2^{1}/_{2}$ years with chlorpromazine alone by using high dosage Some authors had concluded that chlorpromazine was not of value because they used insufficient dosage Chlorpromazine was superior to and more convenient than mephenesin, but it was more toxic, and if doses were given too close together (more often than about every two hours) the effect of the drug was lost (*tachyphylaxis*)

Treatment of tetanus had so far been mostly unscientific Much could be learnt from animal experiments, but final assessment of a drug must be made by carefully designed clinical trials In no other way was it possible to measure whether one treatment was superior to another

Prof E B ADAMS summarised the results of the clinical trials which he and his colleagues had been carrying out at the King Edward VIII Hospital, Durban. Over 200 cases of tetanus in Africans and Indians had been seen in the past two years, and 171 had been included in two clinical trials In the first trial chlorpromazine was compared with barbiturates and in the second trial chlorpromazine was compared with a mixture of chlorpromazine and barbiturates No statistically significant difference was found between the results from the various treatments The mixture of chlorpromazine and barbiturates was easiest to handle and controlled convulsions well Lack of control was seldom a problem and death in convulsions was rare, but yet the patients died Necropsy seldom gave information, and pneumonia was not as common as might have been expected Intoxication of the medullary centres was very probably responsible When the period of onset was less than forty-eight hours the prognosis was bad, and this period was of more value than the length of the incubation period A caution against overtreatment of the mild or moderate cases was given, as they very rarely die and suffer a greater hazard from overtreatment

Dr HUGH GARLAND described the Leeds tetanus unit, which served a population of 3 million and had treated 18 cases of tetanus in the past three years Dr J J L ABLETT, anæsthetist to the Leeds unit, said that of the last 8 patients treated with positive-pressure respiration 3 had died He believed that tetanus "need not kill" They had had deaths from agranulocytosis, pulmonary embolism, and hæmorrhage Treatment with complete paralysis had lasted up to twenty-six days, with an average of two to three weeks Carbon-dioxide narcosis was an important hazard Dr W RITCHIE RUSSELL advocated tracheotomy even in cases of moderate severity, because the results were so good

Answering a question, Professor PAYLING WRIGHT deplored the withdrawal of tetanus toxoid as a prophylactic agent in child-welfare clinics In the discussion, Professor ADAMS said that if patients were kept alive for twenty-six days a 100% survival-rate was possible

Dr A CRAMPTON SMITH described the results of treating 7 cases of tetanus with complete paralysis 3 patients died, but this did not necessarily reflect the true mortality since the series was too small Mortality-rates in other series suggested that the overall mortality-rate from tetanus had declined in the past fifty years probably because of better nursing and general care, but severe grades of tetanus still had very high mortality-rates Curare had been used in the treatment of tetanus since 1860, but it was not until the poliomyelitis epidemic in Copenhagen in 1952 that it was found practicable to treat completely paralysed patients with continuous artificial respiration through a cuffed tube in the trachea The Danish workers first treated a case of tetanus by complete paralysis in 1953 At Oxford the patient with tetanus was first anæsthetised, then paralysed, an endotracheal tube was passed and respiration continued manually until the patient reached hospital, where a tracheotomy was done and a machine continued the respiration Difficulties arose because the patient could not breathe for himself, eat, or communicate He must receive continuous artificial respiration, be fed and turned, and his bronchi must be aspirated Electrolyte balance must also be controlled Every time he moved, a nurse gave an intramuscular injection of curare and hyaluronidase Considerable numbers of patients with various paralytic diseases had been treated in this way, including 32 cases of poliomyelitis with 7 deaths This treatment was expensive, and required large numbers of nurses It had been demonstrated, however, that patients with tetanus could be transported to a centre where they could receive the treatment that seemed to offer the best chance of survival Dr Crampton Smith suggested that this problem should be considered at a national level

Reviews of Books

Homosexuality

Its Nature, Causation, and Treatment CLIFFORD ALLEN, M D, M R C P, D P M, consultant psychiatrist, Dreadnought Seamen's Hospital, Greenwich London Staples Press 1958 Pp 143 15s

Live and Let Live

The Moral of the Wolfenden Report EUSTACE CHESSER, L R C P E London Heinemann 1958 Pp 126 8s *6d*

THE slow progress in disentangling the muddle of laws concerning sexual behaviour is discouraging Now that the Government are hesitating to implement the recommendations of the Wolfenden Committee, on the ground that they have no assurance of popular support for reform, it is to be expected that advocates will resort to the time-honoured practice of pamphleteering It does not detract from the high intentions and serious purpose of the authors of these books to consider their works mainly from the point of view of what they set out to do, and this seems to be to influence the public to move in the general direction advocated by the majority of the Wolfenden Committee These books share the good qualities of being well informed, interesting to read, persuasive without being irritating, and warmly partisan, but not to the point of insobriety They also share a common defect—each would have been very much more effective as two books

Dr Allen's difficulty is that he attempts, mainly by the use of case-studies, to encourage psychiatrists to take a more hopeful view of therapy and to convince patients that their condition can be alleviated These two goals are hard to attain in a single attempt, and the reader's sense of direction may be further confused because the book's aims are not explained until the final paragraph The homosexual patient emerges from the text as an unfortunate figure deserving at least a helpful approach by doctors, which, as many homosexuals know to their cost, is not always forthcoming Dr Allen raises the important question why homosexuals do not follow the much easier path of normal sexual behaviour but, instead, take a road which leads them into such terrible social, personal, and moral difficulties He attempts to show where the reasons may be sought, and his findings may bring hope to many sufferers

It seems a pity that the epidemiology of this condition is not examined more fully Why, for example, has Dr Allen included only 2 women among his 21 cases, and why does he appear to be thinking almost always of men and hardly ever of women? Both these questions illustrate phenomena of considerable importance and deserve fuller examination The book is not entirely free from some rather out-dated analytical modes of thought, manifest in a tendency to offer a stock explanation of common individual propensities For example, it is twice stated that the toddler child's dislike of rice pudding is related to his deprivation at the time of weaning The ordinary reader may well wonder about the author's knowledge of children because, since this oversimplification was first stated, there has grown up a generation of toddlers who know not rice pudding (because of the war) and who have been brought up by mothers with less restrictive notions both about nursery puddings and about insisting on their consumption The result of a nursery Gallup poll about rice puddings might show a majority in favour!

The difficulty in *Live and Let Live* is that Dr Chesser follows the lead of the Wolfenden Committee and attempts to deal with both homosexuality and prostitution at the same time The committee succeeded in keeping the two issues separate, but the same has not been true of the emotional and confused public discussions that have followed In taking both subjects together, Dr Chesser will scarcely add to clarity of thinking, because the "feeling tone" of homosexuality is so much stronger than that of prostitution, and this difference may make the second half of the book appear flat and forced compared with the first

Since his aim is to mould popular opinion and mobilise it in a "more rational" discussion of these problems, it is a pity that he does not consider more fully the significance of the enormous difference to be found, for example, in the strength of feeling shown by ordinary people towards male as compared with female homosexuality, and homosexuality as compared with female prostitution More understanding of these phenomena might make possible the more rational discussion that Dr Chesser and others so earnestly desire

The final sections of both of these books are devoted to constructive reviews of the Wolfenden Committee's proposals in relation to existing law, and they should do something to help secure the public acceptance of that mainly wise and humane report

Florence Nightingale and the Doctors

SIR ZACHARY COPE, F R C S London Museum Press 1958 Pp 163 21*s*

Miss Nightingale was a woman of complex character, who has been pictured in different ways by the several authors who have studied her Sir Zachary's book concerns one aspect of her life—her relationship with the medical profession He has examined it through the medium of her correspondence, diaries, and notebooks This material is voluminous (150 volumes are preserved in the British Museum collection alone), and much in the book has not previously been published Nevertheless, it must be an incomplete record of her activities, of which the most important part was often personal and confidential interviews of which no record survives

Miss Nightingale wrote to, or about, a large number of doctors—eminent and obscure, orthodox and "quack," British and foreign Some of her letters are to international figures, such as Sir James Simpson and Dr John Shaw Billings, others discuss a friend's choice of a family physician Two figures illustrate how her attitude to doctors depended largely on the man Dr John Sutherland, who was the chief medical member of the Government commission sent out to examine conditions in the Crimea, met Florence Nightingale there, and remained her staunch ally for 36 years Their joint efforts completely reformed the Army's standards of housing and sanitation They were the closest of friends—though Miss Nightingale did not scruple to write to him in severe terms if his opinions differed from her own Or to describe him as "a man without a soul" a few years before he died with, it might almost be said, her name upon his lips Very different was her attitude to Sir John Hall, the Inspector-General of Army hospitals Miss Nightingale attributed (perhaps unfairly) most of the evils she found in the Scutari hospitals to "his incredible apathy" And, as her notes of an interview with Lord Panmure prove, she was instrumental in curtailing his military career

To what qualities did Florence Nightingale owe her success? In an age when her sisters were striving for emancipation by emulating masculine activities, she achieved more than any of them She did so by using, to the fullest advantage, very feminine methods She was at pains to develop a warm friendship with many men in positions of high authority Once secure in their esteem, she seems to have used the threat of her displeasure to achieve the ends she sought, yet she was prepared to stay in the background and let the men retain the place of prominence She seldom attended meetings, or swayed large crowds, but she carried her points in private interviews, to which busy and influential personages were constrained to come by Miss Nightingale's rather dubious invalidity She was endowed with a shrewd intelligence, an uncanny gift for accurate and detailed observation, a clear grasp of the significance of statistics, and a tireless energy She was not, however, infallible, and to the end of her days she discounted all evidence which supported the theory of bacterial infection But, whatever her faults, the reorganisation of the Army Medical Services, the redesigning of scores of hospitals, and the introduction of an entirely new idea of sick nursing are lasting proofs of her greatness

Speaking of previous books about Florence Nightingale, Sir Zachary remarks that "few famous persons have been more fortunate in their biographers" That good fortune continue and Sir Zachary is to be congratulated upon a painstakin research that has cast fresh light upon the character of fascinating woman

The Human Ear Canal

ELDON T PERRY, M D, instructor in dermatology, Wayne Stat University Springfield, Ill Charles C Thomas Oxford Blackwell *Scientific Publications* 1957 *Pp* 116 36*s*

THIS very good monograph—mainly about external otitis—is well printed and excellently illustrated The overwhelmin impression it gives is that the human ear canal is a skin-line cul-de-sac and that any inflammation of the canal is, therefore an inflammation of skin—a fact that still needs wider recogni tion Dr Perry warns against the local use of antibiotics i most cases of external otitis, and he emphasises the error o regarding this condition as a single clinical entity, for th external auditory canal is subject to almost as many diseases a skin elsewhere, and each requires its own treatment

Few dermatologists or otologists will feel inclined to spend so much on a book that can be read carefully and comfortabl *in a single evening, but it should form a useful reference boo* in medical libraries

Surgery of Head and Neck Tumors

HAYES MARTIN, M D, associate professor of clinical surgery, Cornell University Medical College London Cassell 1958 Pp 430 137*s* 6*d*

THE first 100 pages are devoted to such general considera tions as preoperative and postoperative management, complications, and disabilities after operation, and there is a useful chapter on the risk of and the disability that follows the sacrifice of important anatomical structures After this, Dr Martin's book is essentially concerned with operative tech niques—imparted more by illustration than by text His book is therefore profusely illustrated, and some of the drawings are good It is less his intention to discuss the pros and cons of the procedures than to describe them nor does he attempt to assess the relative merits of surgery and radiotherapy, either as an adjunct or as elective treatment The value of the book lies in its statement of the methods now in use at the Memorial Hospital, New York

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Industrial Toxicology (2nd ed Baltimore William Wilkins London Baillière, Tindall, & Cox 1957 Pp 376 $10)—The second edition of Mr L T Fairhall's book will be welcomed by many who are concerned with industrial medicine It has two parts, one on inorganic and one on organic substances In each part the toxic agents are discussed in alphabetical order, there are brief notes on the chemical and physical properties of each compound, followed by information on their industrial uses, toxicity, and methods for analysis, and a list of relevant references There are new chapters in which recent information on both pharmacology and toxicology has been incorporated The index is excellent There are one or two obvious omissions—for example, in the section dealing with cadmium, chronic poisoning is barely mentioned In general, however, the standard is high, and the book's usefulness is unquestionable

An Introduction to Pharmacology and Therapeutics (9th ed London Oxford University Press *1958 Pp 327 18s*)—Prof J A Gunn, with the assistance of Dr J D P Graham, has produced a new edition of his popular introduction to pharmacology It has been extensively revised and brought up to date, but with no great increase in length There is very little to criticise, but in the chapter on drugs affecting cardiac muscle quinidine receives rather scant attention, no mention being made of its important use in ventricular arrythmias, and procainamide is omitted altogether The book provides a sound, orthodox, and clear account of the actions of the more important drugs, and their uses, and it will be particularly useful to the student revising for examinations

THE LANCET

LONDON 24 MAY 1958

Malignant Hypertension

The discovery of ganglion-blocking and other potent hypotensive drugs has awakened hopes that with early diagnosis something might be done to check the fatal course of malignant hypertension The physician assessing the value of such drugs should know as much as possible about what happens to the untreated patient A yardstick of this kind has long been overdue, and accordingly a review by Kincaid-Smith, McMichael, and Murphy,[1] based on 197 cases of untreated malignant hypertension observed at Hammersmith Hospital in 1935–55, is particularly welcome In a disease which, left to itself, kills 55% of patients within two months of diagnosis and 90% within a year, the importance of premonitory symptoms cannot be overestimated, and the finding that, as the malignant phase approaches, headache becomes increasingly severe and common should be carefully heeded

The difference between the benign and malignant phases of hypertensive disease is now regarded by many as one of degree, but opinion has never been entirely unanimous This question hinges on the pathogenesis of the essential lesions of the malignant phase—namely, focal fibrinoid necrosis of terminal arteries and proliferative endarteritis of slightly larger vessels When Goldblatt's work opened up hypertension to experimental study it was soon found that these lesions did not occur in the kidney distal to the clamp on the renal artery[2,3] From this it was concluded that the lesions could not be caused by a circulating toxin, nor by simple ischæmia, nor by simple vasoconstriction due to a circulating pressor substance, but must in some way be related to the increased intra-arterial tension It seemed that the determining factor was a sudden strain imposed on the vessel wall by a combination of severe vasoconstriction and the accompanying rapid rise in blood-pressure This simple concept has stood up fairly well to the test of subsequent clinical experience and experiment. Lesions have been shown to follow sudden distension of the arterial tree, in animals by intravenous injection of saline,[4,5] and in man by operative relief of coarctation of the aorta[6] Necrosis has also been observed in the pulmonary arteries in mitral stenosis[7] By means of cranial windows the process has been followed in some detail in the brain of the hypertensive rat, and shown to be closely related to intense arterial contraction which disappears rapidly if the hypertension is abolished[8] The dramatic effect of lowering the blood-pressure has also been demonstrated in man[9] In their own material the Hammersmith workers find further corroborative evidence in the absence of arterial lesions from areas of kidney supplied by narrowed atheromatous arteries, and they do not dispute that the evidence shows that excessive intra-arterial tension can cause arterial necrosis Nevertheless they are unwilling to accept the conclusion that the arterial lesions in malignant hypertension are simple results of mechanical strain, and they seem to incline to a dual hypothesis according to which some toxic or even allergic injury, in addition to high blood-pressure, leads to " exudative angiitis "

A dual hypothesis of this kind of course implies that malignant hypertension must be regarded, not simply as a grade of severity which may develop in any sort of hypertensive disease, but as something differing in kind from the benign form, much more obscure and disturbingly akin to the primary nephritis with which it was so long confused In malignant hypertension fibrinoid necrosis can be found in afferent glomerular arterioles distal to interlobular arteries which are greatly narrowed by proliferative endarteritis The Hammersmith workers argue that hypertension can hardly be responsible for the former lesion, because the narrowing, like an arterial clamp, should act as a barrier But this assumes that the lesion in the interlobular artery precedes that in the afferent glomerular vessel There is in fact no evidence that it does It is more likely that the two lesions are responses to a simultaneous insult Similar narrowing of the lumen of interlobular arteries by simple or fibrinous exudate is commonly observed both in man[10] and experimentally, and endothelial proliferation is probably a stage in the repair of this exudative lesion There is no evidence to show how long fibrinoid necrosis in the more distal vessels can persist before repair occurs Kincaid-Smith et al find that, although the arterial pressure tends to be very high in the malignant phase, there are exceptions and the pressure is not impressively higher than in a control series of patients with benign hypertension In fact the mean difference in pressure in 25 matched pairs of patients with benign and malignant hypertension was no greater than 12 mm Hg But the control group was drawn from patients with retinitis, in whom, clinically and post mortem, there was no evidence of malignant hypertension Benign hypertension, on the estimate of the Hammersmith group, is about a hundred times as common as the malignant form, and it may be argued that the minority of patients with benign hypertension who come to post-mortem in a teaching hospital is, statistically speaking, a selected group which may include an undue proportion of severe cases The mean blood-pressure in this group was 213 mm Hg systolic and 122 mm Hg diastolic

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[1] Kincaid-Smith, P, McMichael, J, Murphy, E A *Quart J Med* 1958, 27, 117
[2] Wilson, C., Pickering G W *Clin Sci* 1938, 3, 343
[3] Wilson, C, Byrom F B *Lancet* 1939, i, 136
[4] Byrom F B, Dodson, L. F *J Path Bact* 1948 60, 357
[5] Masson G M C., Corcoran, A C, Page, I H *Circulation*, 1951, 4, 467 (proc)
[6] Benson, W R., Sealy, W C. *Lab Invest* 1956, 5 360
[7] Hicks, J D *J Path Bact* 1953, 65, 333
[8] Byrom, F B *Lancet*, 1954, ii, 201
[9] Pickering, G W, Wright, A D, Heptinstall, R. H *ibid* 1952, ii, 952
[10] Ellis, A *ibid* 1938, i, 977

The fact that in some patients very high blood-pressure may persist indefinitely without causing serious symptoms, while in others malignant symptoms appear before the pressure has risen to particularly high levels, does not invalidate the general proposition that malignancy is essentially an expression of severity In assessing severity in hypertensive disease it is necessary to consider not only the level of blood-pressure but also the intensity and nature of the underlying vasoconstriction[3 8] The available evidence suggests that the individual lesion in malignant hypertension owes its origin to a demonstrable functional abnormality which develops quite suddenly in overstimulated, overstretched arteriolar muscle, and if this essentially local disturbance is widespread or persistent enough the disease enters the malignant phase The fact that such a transformation is rare is perhaps remarkable, but no more so than the adaptability of arterioles in benign hypertension The simple physical concept of malignancy must of course remain tentative as long as so little is known about ætiology Nevertheless it may be unwise to reject it merely because it is simple, and still less because it is physical In the last analysis most if not all biological reactions are physical

Bones, Genes, and Pregnancy

ORTHOPÆDICS, though it has a long history, has been recognised as a surgical specialty only quite lately In Britain its birth is customarily dated from the work of HUGH OWEN THOMAS, who died as recently as 1891, fifteen years after KOCH's discovery of the cause of tuberculosis, and rather more than fifteen years before vitamin D was heard of Orthopædics in THOMAS' day was very different from orthopædics now Rickets was common, and its manifestations produced much of the surgeon's daily work Tuberculosis and osteomyelitis, not fully understood, wrought dreadful damage in joints and bones Poliomyelitis, then a mystery, led to contractures and crippling Injuries, apart from those induced by occupational hazards, were relatively few Since then orthopædics has seen a succession of dramatic changes Bone-grafting and bone banks have been established, and new materials introduced for pins, pegs, and prostheses Pyogenic infections of bones and joints have been trounced by chemotherapy and antibiotics, though it must be admitted that osteomyelitis is in some places staging something of a comeback, having called up its reserve forces of immune organisms Tuberculosis can now be treated very effectively, and it looks as though the days of poliomyelitis may be numbered On the other hand, the internal combustion engine has produced an appalling increase in the practice of traumatic surgery, and degenerative arthritis has become a greater problem in an ageing population

In all this change, one orthopædic responsibility has remained more or less constant The congenital deformities—club-foot, dislocated hip, and the like—which helped to give the specialty its name are still with us indeed, they are possibly more common because of the lower infant mortality and the better care of children Though the more striking genetically induced catastrophes have been documented, the commoner bony deformities need a great deal of further study But we are nowadays coming to realise that genetics is perhaps only part of the story By subjecting laboratory animals to stress during pregnancy we can now produce bony defects in the offspring just as surely as Nature can produce them by the union of two ill-suited germ cells This type of work is still in its infancy, and there is scope for a great deal of further effort

Last September the Société Internationale de Chirurgie Orthopédique et de Traumatologie, at its meeting in Barcelona, made this statement

> "In view of the serious problem presented by congenital deformities and the obscurity of their causation, this Congress recommends that its members should take the following action in their respective countries
>
> 1 To endeavour to establish research units in appropriate centres in collaboration with other interested workers, such as obstetricians, pædiatricians, and embryologists
>
> 2 To point out to their Governments the social and medical importance of the problem and to seek the financial aid necessary for the prosecution of research
>
> 3 When and where it seems desirable, to ask for the institution of statutory notification of disorders—rubella and diabetes for example—believed to be important in the ætiology of congenital disorders"

These propositions are in line with the modern idea of a concerted assault on a problem by the adherents of many disciplines—tactics that have already paid in many other medical fields Our knowledge of the processes involved in skeletal growth have matured very rapidly by following this prescription, and it is to be hoped that a similar result will attend the proposed attack on congenital deformities GREEN[1] has convincingly argued that more money and effort should be devoted to research in orthopædics, and there can be no doubt of the importance of this particular cause

Radioactivity and Public Health

Too often the subject of atomics is treated with the reverence accorded to a mystical cult, with the furtiveness appropriate to industrial restrictive practices, or with the secrecy which national security may or may not require Yet what we are witnessing is perhaps the greatest ecological change since the recession of the polar icecap at the end of the last Ice Age Even the small amount of research already done has demonstrated the selective uptake of radioactive isotopes by certain aquatic and terrestrial plants, the varying sensitivity of different forms of life to increasing radiations, the biological concentration of some isotopes in the tissues of the animal body, and their effect on genetic mutations We are standing on yet another fringe of the unknown, not as Man alone, but with the whole range of living things grouped around us in a symbolic question-mark It is against this enormous background that we have to examine our more local problems of radioactivity

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[1] Green, W T *J Bone Jt Surg* 1957, 39A, 675

The decision of the Liverpool City Council to buy apparatus for measuring radioactivity in their water-supplies not only illustrates the movement of local authorities into this new territory but also raises wide issues—what and why and when and how and where and who? In Liverpool the city council are cautious in feeling their way into atomics, but they think that the time has now come to build up a mosaic picture of radioactivity as it may affect their population—to establish their datum line of background radiation levels, to watch for the changes and record the facts, and to check the food that the people of Merseyside eat, the air they breathe, the water they drink That project will carry their investigations far afield, for their present water-supplies come from Wales and Lancashire, and their future schemes include using the River Dee as an aqueduct, with all the extra possibilities of radioactive industrial effluents There is, of course, nothing novel about far-flung interests Manchester keep check on their Lake District reservoirs at Thirlmere and Haweswater, and other large water undertakers take the same precautions There is nothing novel about abstracting water below the outfalls of potentially radioactive waste much of London's drinking-water is taken out of the Thames below the outfalls of the Harwell, Aldermaston, and Amersham atomic establishments The novelty lies in the growing emphasis on the need for independent control, and the need to come to terms with changing ways of life

In the matter of ways and means, it is clear that though some of the larger municipalities, to discharge their responsibilities, may create comprehensive radiochemical and radiobiological laboratories, such action will be far beyond the resources of the majority Probably the time is not far distant when all public-health authorities will be expected to maintain routine monitoring in their districts, but qualitative analyses are not so easy, and interpretation of the factual data can be harder still Perhaps the larger municipalities will extend their facilities to their neighbours, both for the analytical work and for interpretive advice—provided they can attract staff of high enough calibre to hold consultant status But there are possible alternatives For example, the public analysts may see in atomics a fresh opportunity for expanding their professional business, particularly in the commercial markets Specialised agencies for providing radiological protection have already entered hospital and industrial practice, and they seem likely to increase in number and value The universities, on the other hand, should avoid becoming too far involved in the routine work of the extramural world, and it would not be sensible to look to them to provide the services required

The United Kingdom Atomic Energy Authority occupy a unique position They certainly have the equipment, the laboratories, the concentration of knowledge, and the specialist staff required for their own purposes, but just how far they can be expected to offer help outside their perimeter wire is still debatable They are still hypersensitive about their safety obligations under the Atomic Energy Act, they remain much preoccupied with their own industrial medical service, and they are feeling their way in public relations Acting on a recommendation by the Fleck Committee, they have now appointed a committee, under Sir DOUGLAS VEALE, to advise them on the training and provision of "health and safety" staff not only for their own purposes "but also to meet the needs of the nation as a whole" (see p 1137), but it would be unrealistic to expect an adolescent industry to undertake unlimited commitments Though they have agreed to make their resources available to some of the smaller public-health authorities in the vicinity of reactor establishments, obviously there must be a geographical limit, both for the A E A to foster good personal contacts, and for the public-health authorities to expect the A E A to provide a free monitoring service Again, while it is reasonable to expect cooperation from the A E A in monitoring their own effluents, and to help in estimation of natural background levels and fallout effects, they could hardly be asked to supervise the radioactive wastes from other industries, hospitals, and laboratories in the area The public-health authorities will rightly be expected to do what might be called their own dirty work

The increasing industrial use of radioactive isotopes opens up another possibility for routine supervision Various Ministries already have monitoring responsibilities under the Atomic Energy Act, and some have appointed a radiochemical inspectorate Expansion of those departments, with their possible absorption into the Factory Inspectorate, would be one way to provide nation-wide monitoring But this might well mean that attention was concentrated on the industrial problems of radioactivity, whereas we should be thinking of the total load of radioactivity, from whatever source If, for this reason, it is accepted that the public-health authorities are the proper bodies to keep a watchful eye on the health and safety of the whole community, might it not be better if the expert help they will need were given by the Public Health Laboratory Service, so long a valuable companion to the medical officer of health in his day-to-day epidemiology? The personal contacts are there, the confidence is there Opinions differ on the future of the P H L S[1], but if it is to remain outside the National Health Service it could logically be extended by adding a radiochemical section Specialist staff could hardly be assigned to every laboratory, but some convenient regional grouping might be possible, as with some other specialised techniques Quantitative measurements, qualitative analyses, and interpretation could alike be made with a bias towards the practical work of the public-health authorities, whose cooperation would be implied, and whose duty to safeguard the public health in this as in its other aspects would remain as clear as it is strong

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[1] *Lancet*, April 26, 1958, p 909

Annotations

LIBERTY, EQUALITY, AND HEALTH

OVER the years opposition to health legislation has been steadily weakening and falling back on untenable positions Its deepest ditch has always been that health measures curtail the freedom of the individual In an interesting review of the organisation of medical care during the past fifty years Prof R M Titmuss[1] suggests that even this is based on a misconception The summits of health legislation in these years were of course the Acts of 1911 and 1946, and in his view both of them only substituted one form of collectivism for another and each offered increasing freedom to a growing circle of doctors and patients

The development of scientific medicine since the beginning of the century, accelerated by two world wars and what Professor Titmuss describes as the scientific discovery of malnutrition in the 1930s, made the reorganisation of medical care inevitable Advances, which were swift and seldom simple, ranged from new fundamental concepts such as the new ideas of Freud to complicated techniques of the laboratory and operating-theatre, and to potent new drugs Their complexity made specialism a necessity Their cost raised problems of distribution that were thrown into sharp relief by new statistical and social methods which showed the inequalities of health among different groups of the population Emphasis began to shift from the environment to the individual patient, from the public-health officer to the general practitioner, though general practice at the time was in a sorry way Professor Titmuss estimated that in the days before the panel only 10–20% of the population were able to afford to have a private doctor for the whole family For the rest of the population there was club practice for the breadwinners The women, children, and old people had to make do with the outpatient departments of the voluntary hospitals, the poor-law institutions, and the sixpenny doctors One unhappy result of this sporadic medical care was people's reliance on the " secret remedies " which turned many of them into " permanent medicine swallowers ", a national habit which, as we know to our cost, still persists

Contract practice, in Professor Titmuss' view, was also one of the chief reasons for the doctors' distrust of lay administrators which was shown in their negotiations with the Government in 1911 and in 1946 Indeed the present structure of the National Health Service, he suggests, owes more to the opinion of doctors than to political and public opinion As he assesses the situation, in 1945 many of the consultants, foreseeing the coming bankruptcy of the voluntary hospitals, the threat of greater local-government control, and the probable harmful effects for doctors as well as patients of the rise in the private costs of health, shrewdly led the profession into the National Health Service However that may be, the Act of 1946 extended health enfranchisement to women and children and the middle classes Professor Titmuss considers that the service would perhaps not have been so comprehensive but for the nation's post-war mood for justice and equality of opportunity But it was also, in his view, a renewal of the argument for the freedom of doctor and patient To see it solely as a collectivist device for the benefit of the working-classes is too simple, and he believes that the middle classes have benefited even more, and the doctors most of all

GOING TO HOSPITAL WITH MOTHER

THE children of this country are ill less often than ever before in our history But for the many who still fall seriously ill what is the best type of care to provide? Wider recognition of the emotional sufferings of little children separated from their mothers has led thoughtful doctors and nurses to promote various reforms Elective operations can be postponed until a stay in hospital is a less disturbing experience for the child—that is, until he is over the age of 5 or 6 Daily or unlimited visiting is becoming much more common in children's wards Mothers are now sometimes admitted with their young children, and, finally, more illnesses are being treated in the home

The first film made by Mr James Robertson, of the Tavistock Clinic, *A Two-year-old Goes to Hospital*,[1] helped to draw notice to the need for these improvements This moving picture of a young child's suffering in hospital caused a painful emotional struggle in many people, who had to recognise that their conscientious efforts to help had caused avoidable suffering When Mr Robertson's second film, *Going to Hospital with Mother*, was shown to a Press audience a few days ago it was preceded by excerpts from his first film, and the juxtaposition emphasised convincingly the contrast between the emotional states of two young children admitted to hospital for the same operation For the second film is of a mother and child entering the children's ward of Amersham General Hospital, where nearly half the under-5-year-olds are accompanied by their mothers Making allowance for differences in temperament, there can be no doubt whatsoever that the little child who had her mother with her overcame a more serious physical reaction to the operation with far less emotional disturbance than the child whose mother could spend only a short time with her each day Even the most sceptical audience could hardly fail to be impressed by this second film, which is technically of a high order and well constructed to convey its message

But bringing mother into hospital with the child is not enough in itself The film makes clear that a big change of attitude is called for—particularly in the nursing staff In a ward where mothers and children are admitted together those in charge must be able to appreciate the mother's anxiety and to help her with it Not only has the mother an ill child to worry about, she has had to leave her husband and possibly other children to fend for themselves She may also have conscious or unconscious anxieties herself about hospitals, and medical or surgical procedures This maternal anxiety can, and does in certain cases, communicate itself to the child or other mothers But, provided the mother can be given understanding support, there is no doubt that the child will benefit greatly from her presence and comfort at a difficult time The mother will, at the same time, gain confidence in her relationship with her child, through encouragement to help him when he is ill and needs her most

The ward-sister who can find satisfaction in helping mothers to help their children is unfortunately still too rare, though if more doctors were far-seeing enough to give the lead hidden reserves would surely be uncovered But a wholesale change in the attitude to childhood illness could not be achieved without changes in the training of nurses and doctors It is the nurses who fear most that they will lose their function, yet in fact the way is being opened for them to play a much bigger part in the lives of their patients

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[1] A lecture on health, in a series on Law and Opinion in England in the Twentieth Century, given at the London School of Economics on April 29 The series will be published later under the general editorship of Prof Morris Ginsberg

[1] See *Lancet*, 1952, ii, 1122

Thinking beyond the lesson of this film, we can recognise that many more young children who are ill could be nursed at home, given adequate special assistance Most mothers would probably be much less anxious in their own homes, where they can be helped to fulfil their many responsibilities without a conflict of loyalties Clearly it is least disturbing emotionally for the sick child to have no extraneous difficulties, such as separation from home or mother illness itself is enough of an anxiety

Moreover, from the physical viewpoint, hospitals are by no means always the best places in which to be ill at any age Perhaps Mr Robertson will make another equally skilful and convincing film called *Being Ill at Home*?

THE ASIAN INFLUENZA EPIDEMIC

LAST week the Section of Epidemiology of the Royal Society of Medicine discussed the recent world-wide epidemic of influenza Dr A M -M Payne, of the department of endemo-epidemic diseases of the World Health Organisation, described the surveillance of last year's epidemic, the first widespread epidemic to arise since W H O set up a network of laboratories and listening-posts for an eventuality of this kind By a curious stroke of fate, however, the epidemic started in Communist China, which is not a member of W H O As a result, two or three valuable months were lost before W H O could give warning that a new influenza virus was about and that it was likely to spread and cause epidemic disease Within seven months the new virus had spread to almost every country in the world, and in many places attack-rates of 20–40% of the population were reported Overcrowding had a striking effect in increasing the attack-rate, and almost everywhere it was found that people over 60 were less likely to be attacked than younger people There has been much speculation whether this sparing of older people might be the result of infection in earlier life with a virus immunologically similar to the present Asian virus[1], but the feeling of many who took part in last week's discussion was that older people were less exposed to infection

This point was carefully discussed in a thoughtful paper by Dr J C McDonald, who summarised a series of investigations of the epidemic in this country There was a striking association between the onset of an epidemic focus and the opening of schools in that area Schoolchildren then brought the infection home, as was easily shown by study of the onset of primary and subsequent cases in families There was a lower incidence of influenza in families without schoolchildren, and if families without children were considered alone there was no sparing of older people compared with younger members of the same family Taken together these findings suggest that older people were spared because they were less exposed to infection There is growing evidence, however, that although older people were relatively free from influenza during last autumn when the epidemic wave was at its height in this country, infections with the same virus were continuing during the early part of this year Deaths probably due to influenza showed two peaks, one in the autumn and one in the early part of this year, and, in the second wave particularly, there was a high proportion of deaths in those over 65 The influence of weather and the significance of the sparing of older people during the first wave remain important subjects for investigation

On the key question, "What will the Asian virus do next winter?" both Dr Payne and Dr McDonald thought that after this burst of activity it would now settle down to a normal existence

SUDDEN BLINDNESS

ONE of the less common emergencies that face the neurosurgeon is sudden visual failure, either in one or, occasionally, in both eyes The diagnosis between surgically operable and other conditions may not be easy, while it is notorious that tumour within the sella turcica may give rise to a bizarre picture that is usually mistaken for meningitis, subarachnoid hæmorrhage, or sagittal-sinus thrombosis In a helpful article Uihlein and Weyand[1] analysed the causes of unilateral loss of vision of 310 cases at the Mayo Clinic Ophthalmological conditions accounted for 50% of the cases, while in 39% there was a lesion involving the retrobulbar portion of the optic nerve Uihlein[2] reviewed those cases in which there was acute visual failure and found that the non-ophthalmological causes were, in order of frequency, pituitary tumour, glioma of the optic nerve or chiasma, aneurysm, "parasellar lesion", carotid thrombosis, distension of the third ventricle by hydrocephalus, chiasmal arachnoiditis, fracture of the anterior cranial fossa, tumour of the base of the skull, and pseudo-tumour cerebri The most important of these is the commonest—pituitary tumour The effects of pituitary tumours include acute complications,[3] of which the most dangerous is "apoplexy of the pituitary gland" In this, Brougham et al[4] found that extensive necrosis or hæmorrhage in a pituitary adenoma resulted in the sudden onset of drowsiness followed by stupor or coma, severe headache with nuchal rigidity, ocular palsy, and sometimes amblyopia or hemiparesis The cerebrospinal fluid contained blood or was xanthochromic with an increased number of white blood-cells and commonly an increased amount of protein Indications of pituitary insufficiency may be the only early feature distinguishing the disorder from acute adrenal insufficiency, a temporal-lobe pressure cone, or the effects of an epileptic convulsion Even after investigation in hospital, cavernous-sinus thrombosis, meningitis, or subarachnoid hæmorrhage may be reasonable diagnoses The condition is extremely dangerous, and saving of life is the first consideration As long as the clinical course moved towards recovery, Brougham et al pursued conservative treatment They suggested that with adequate supportive measures some patients might reach a plateau of improvement from which some of them might be rescued List et al[5] described three cases of a similar syndrome with a satisfactory outcome They recommended operation provided there was no hypopituitarism, but if severe panhypopituitarism dominated the picture early surgical treatment was inadvisable Even diagnostic procedures may lead to sudden peripheral vascular collapse Investigations should include blood-sugar curves and estimation of electrolytes A ventriculogram may furnish valuable information[6]

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[1] See *Lancet*, April 19, 1958, p 833

[1] Uihlein, A, Weyand R D *Arch Ophthal*, *Chicago*, 1953, 49, 261
[2] Uihlein, A *Brit J Ophthal* 1958, 42, 157
[3] *Lancet*, April 12 1958, p 780
[4] Brougham, M, Heusner, A P, Adams, R D *J Neurosurg* 1950, 7, 421
[5] List, C F, Williams J R, Balyeat, G W *ibid* 1952, 9, 177
[6] Jefferson, G *Proc R Soc Med* 1940, 33, 433

Discussing the causes of acute visual failure, Uihlein described five cases in which visual improvement followed prompt operation As long as any vision at all remains, surgery may offer considerable hope of restored vision Where complete blindness has resulted the prognosis is so much worse, but even then vision may occasionally be restored by prompt intervention Where blindness is accompanied by acute hypopituitarism the risk must be carefully weighed, and the neurosurgeon's judgment is stretched to its utmost

ANÆMIA DUE TO ANTICONVULSANT DRUGS

In 1954 Badenoch [1] demonstrated megaloblastic anæmia in 2 epileptic patients, and Hawkins and Meynell,[2] reporting a similar case, suggested that the phenytoin ('Epanutin') given for treatment to all 3 patients was the cause Later in 1954 Chalmers and Boheimer [3] described a similar incident in a patient who had had barbiturates and phenytoin for some years but for the previous six months had had primidone ('Mysoline') Since then several cases have been reported, and isolated reports continue to appear for example Kidd and Mollin [4] reported a case associated with phenytoin and another with phenytoin and primidone treatment, and Barker [5] and Varadi [6] have lately reported further cases in our columns Newman and Sumner [7] reported a case associated with primidone but reasonably concluded that megaloblastic anæmia due to anticonvulsants is a rare complication that should not deter physicians from using phenytoin and primidone, now the two most effective anticonvulsant drugs These reports make it important to find out the true incidence of megaloblastic anæmia in patients with epilepsy receiving anticonvulsants, whether there are any early indications that the drugs are causing interference with hæmopoiesis, whether such signs can be corrected, and, if so, whether this benefits the patient

To answer such questions, Hawkins and Meynell [8] have carried out a series of investigations in a colony for epileptic and mentally defective patients

They studied 72 epileptic patients (40 male and 32 female) who were all receiving anticonvulsant drugs—phenobarbitone, phenytoin, and primidone, alone or in combination For controls they used 30 non-epileptic mental defectives living in the same colony, and 30 healthy persons, mostly medical students and hospital staff Few patients were actually anæmic, but significant macrocytosis was found Of the epileptics a third had a mean corpuscular volume (M C V) of 94 c μ or more, and the mean in all the epileptics was 92 2 c μ (S D =4 51), whereas in the normal controls the mean was 86 6 c μ (S D = 2 53) In the 30 patients who lived in the same colony but did not have epilepsy the figure was 88 7 c μ (S D =2 58) All these differences were statistically significant Further analysis showed that of patients receiving both phenobarbitone and phenytoin, 45% showed macrocytosis of the erythrocytes, in patients on one drug the figure was 34% for phenobarbitone and 27% for phenytoin, 2 out of 3 patients on phenytoin and primidone had macrocytosis, but all 4 on primidone alone were normal There did not appear to be any significant dietary deficiency among the patients, and there was no evidence of liver disease The incidence of macrocytosis was unrelated to the number of fits

There was indeed little doubt that the anticonvulsant-drug therapy was the cause of the macrocytosis Hawkins and Meynell investigated the serum-vitamin-B_{12} levels in a group of epileptic patients and found normal figures, they took 6 with macrocytosis and gave them 100 μg vitamin B_{12} subcutaneously weekly for two months, but the macrocytosis remained unaltered There was therefore no indication of vitamin-B_{12} deficiency Tests to determine effects of folic-acid absorption or tissue depletion of folic acid were carried out by Girdwood's method [9] and no abnormalities were found But when 20 mg of folic acid a day was given orally for a month to 6 patients with macrocytosis, the M C V values fell towards normal in every case

Actual drug-induced macrocytic anæmia is, as suspected, uncommon Hawkins and Meynell had been studying 170 epileptic patients over two years and found only 8 cases of macrocytic anæmia among them

6 of the 8 were being treated with a combination of phenytoin and phenobarbitone, 1 was on phenytoin alone, and 1 on primidone and phenytoin In 4 the anæmia was severe, with hæmoglobin levels from 22% to 47%, and all these patients had typical megaloblastic marrows, of the others 2 were reported as macronormoblastic and 1 as "hypoplastic", and 1 was not examined

Their patients were given vitamin B_{12} and, as in other trials, the response was variable, 5 of the 8 patients responded well, but 3 needed folic acid The anticonvulsant drug was kept on at the same dose except in 1 patient whose phenytoin was stopped and phenobarbitone given instead Folic acid seems to be the most suitable anti-anæmic drug, and Hawkins and Meynell suggest that a daily dose of 5–10 mg provides sufficient protection, with this dose there has been no tendency for neurological complications to appear

Hawkins and Meynell draw attention to the remarkable improvement in the epilepsy when the anæmia was treated, and their case-reports are indeed striking

For example, a man who had previously had 2–3 attacks of minor epilepsy a month for twenty years had no further attacks after treatment of his anæmia and maintenance on folic acid for three years, and a man aged 21, who had at least 3 major attacks daily, has had a two-year period free from attacks after treatment of his anæmia On the other hand treatment of the anæmia had no effect on the number of fits in an imbecile epileptic

Hawkins and Meynell hold that "blocking of vitamin B_{12} and folic acid is an important factor in lowering the threshold for the cerebral discharge producing the epileptic attack" This blocking presumably interferes with the synthesis of ribonucleic acids—and at an early stage in the process, according to current views, since vitamin B_{12} and folic acid can overcome the effect

From a practical point of view this report shows that it is worth examining at regular intervals the blood of epileptic patients who are receiving regular treatment with anticonvulsant drugs To detect the toxic effect in its early stage, it is necessary to estimate the mean corpuscular volume This estimation is carried out in most laboratories by Wintrobe's method, which involves taking a sample of venous blood Some methods require only finger-prick blood, for example, Shils et al [10] have described a micromethod using the usual 0 02 ml "hæmoglobin" pipette, and such a method might be more convenient in an epilepsy colony If the M C V is high and continues to rise, treatment with folic acid in addition to the anticonvulsant is indicated Since the epilepsy itself benefits from the correction of the anæmia, regular ordinary blood-counts should also be part of the programme of control

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Special Articles

EARLY DISORDERS OF THE MOTHER-CHILD RELATIONSHIP *

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THE importance of early childhood experiences in the genesis of psychoneuroses in adult life is widely recognised and indicates where the first steps should be taken to prevent such emotional breakdown The child-guidance clinics, overworked and understaffed, complain that even their cases often come too late So we turn to the very earliest years of life and already find, although our clinical experience in "*infant psychiatry*" is not yet extensive, much to interest those concerned with the health of children

Normal Mother-child Relationship

The mother-child relationship may be described as the sum total of the thoughts, feelings, attitudes, and resultant behaviour of a mother towards her child

Where human psychology is concerned, "normal" is almost a forbidden term, yet some attributes of mothering seem to be of its essence, though taken so much for granted that we become aware of them only when absent or distorted Although most of these are relevant for the whole range of childhood, the emphasis shifts with increasing age

Firstly, and basically, there is mother-love, to which an essential corollary is the mother's enjoyment of her child Next there is protectiveness of the child from psychological and physical traumata Although a mother's mood may fluctuate within fairly wide limits, there should be an underlying consistency of attitude We do not expect what is forbidden on Monday to be condoned on Tuesday

A mother's reactions should be appropriate to a given situation, and we are startled when confronted, for example, with real amusement as a response to a child's severe distress A mother should perceive her child as a separate person, she should not make the child simply an instrument of her own ambitions (Stone 1955)

Disordered Mother-child Relationship

As soon as we attempt clinical description, it is proper to ask what is known of the normal range of interactive behaviour between mother and child It must be emphasised that this is not the same as the "milestones" of child development Without in any way disparaging the pioneer observations of Gesell and others in this field, we can say that these workers studied the developing child, as it were under a psychological microscope but to a large extent in vacuo, with little reference to the development of the child's primary interpersonal relationship with its mother

It takes assiduous practice to be able to observe, let alone record, everyday interaction between mother and child (Escalona 1953) such as confronts us daily in clinic and consulting-room, but which we tend to ignore as irrelevant

DISTURBANCES IN EMOTIONAL CONTACT

Lack of Contact

Mother and child are together yet remain two separate unrelating people The toddler is exploring the surgery or examining some toys, and the mother is telling her story to the physician, but nothing happens between them This is quite abnormal, even for a worried mother in a strange setting, because ordinarily the more threatening the environment the more perceptive is a mother of the minimal distress signals emanating from her child Interruptions and distractions are the rule The appeals to the mother to "see what I've done", to "lift me, I'm tired", to "take me to the bathroom" are often conveyed by minimal cues, even without words, but, just as a mother responds even while asleep to the infant's first whimper, so here the maternal antennæ pick up the distress signals and take appropriate action

The picture has a different look where a mother and infant are concerned (Levy 1951) Here we are inclined to describe what we see figuratively—e g , "That woman handles her baby like a parcel" By this simile we record the absence of a whole range of maternal activities which ordinarily are in action Even during a consultation the mother will make her infant more comfortable, address it, smile at it, soothe it to sleep, and so forth In the absence of all this the child seems to have an inanimate quality—"like a parcel" This impression of "emotional distance" is sometimes strengthened by the mother's avoidance of the use of the child's name or the more common "he" or "she", instead she may refer to "it"

Excessive Contact

By contrast we have a situation in which for long stretches of time there is never a break in contact This is the mother who, even as she is talking to the physician, is all the time touching, caressing, fondling, stroking, or hugging her child, but automatically and not in response to the infant's actions, almost as if the child were a pseudopodium, an extension of her own body (Escalona 1948) Sometimes when one is listening to her story, it is quite difficult to tell whether she is describing the symptoms of the baby or of herself

DISTURBANCES IN PROTECTIVE FUNCTIONING

Excessive Maternal Anxiety

This mother is convinced that there is something wrong with her infant and, despite repeated negative clinical findings and abundant reassurance, persists in her belief Her complaints tend to be vague or subjective, her infant may be thriving, but her intense anxiety is real enough, and in search of help she migrates from family doctor to health visitor to pædiatrician and back again

This is not just an anxiety state in a woman who happens to be a mother, for her anxiety is focused exclusively on her child It should be remembered that maternal anxiety is a normal component of the protective function and only when it becomes inappropriate in degree or context should it be regarded as pathological The assessment of this situation calls for the keenest clinical acumen, and most of us have encountered just such a case where a mother's intuition in the end proved superior to expert opinion

In reaching a decision one must balance carefully the data provided by sensitive history-taking, an assessment of the mother's personality, and a careful physical examination of the child Once again the disorder can often be diagnosed by observing the mother's handling of the child We may describe this as follows "You would think her baby is made of porcelain", or "She holds it like a fragile doll", as if it might break in her hands This behaviour persists, unlike the uncertain tentative handling by the mother of her firstborn When the child grows a little older, we begin to see the widely recognised picture of maternal overprotection, where the mother anticipates every possible and impossible danger, is oversolicitous about the child's health, tends to overfeed, and so on

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*Based on a lecture given to the Scottish child-health group of the Society of Medical Officers of Health in February, 1957

Lack of Protective Functioning

It is rare to witness this deficiency in crude form, but at times one encounters a child who is constantly exposed to physical dangers—fire, open windows, traffic, and so forth A less obvious variant of unprotectiveness, however, is not so rare failure to protect the child from its own overwhelming emotions—e g, the mother who allows mounting rage to proceed to a stage of panic, who demands standards of performance well beyond the child's maturity, who uses terrifying threats and warnings or exposes the child to scenes of violence

During a consultation a mother observed in the presence of her 6-year-old son "Of course he's an adopted child", and in response to my query she answered "Oh no, he doesn't know anything about it" This, by the way, was not a stupid woman Indeed, I have found little evidence to suggest that the mother's level of intelligence is a significant factor

Sometimes a mother makes almost adult demands of her baby "I have always laid great store by encouraging the child's independence In fact I have always trained her to make her own decisions As soon as she could talk, at 15 months, I would make her decide at breakfast whether she wanted her egg boiled or poached"

Another striking instance of disordered protective functioning was the mother whose 2-year-old daughter was so pale (largely because of a feeding problem) that the mother always put rouge on the child's cheeks before taking her out for a walk

Reactions of the Child

Sometimes the child does not seem to react to these disorders in relationship For example, in routine baby or toddler clinic examinations our own observations of maternal attitude and handling may strongly suggest that all is not well, yet the mother has no complaints, and the child is in excellent health and spirits Later we may find that another child in the same family and under very similar conditions is far from well It should not surprise us too much that infants are born with different degrees of sensitivity to emotional stimuli, the occasional child reacting violently to minimal stresses Glover (1953) has rightly made a plea for careful follow-up studies of these infants, postulating that these behaviour patterns may be the very first hints of psychological instability

In other cases where there is clear evidence of disordered mother-child relationship the child's "symptoms" may be entirely subjective, at any rate at first, but sooner or later the baby tends to show disorders of crying, of sleeping, of feeding, and of bowel function, alone or combined The child may cry all the time or not at all, refuse to sleep or sleep excessively, show no interest in food, vomit or ruminate, or have bouts of diarrhœa Where an allergic diathesis is present, the response may take the form of infantile eczema or "wheezy bronchitis" There is great difficulty in diagnosis here in that these symptoms may also present in a large range of medical and surgical diseases of infancy The attempt, however, should always be made to diagnose a disordered mother-child relationship by recognising its positive signs and not to infer the diagnosis by failing to detect clinical signs in an infant The presence of such signs may not be the cause of the symptom in question, their absence may only mean that the lesion is clinically undetectable At a slightly older age other responses appear—e g, temper tantrums, breath-holding attacks, withholding of fæces, and excessive and persistent fears

Technique of Interview

At least half an hour is required, and for the physician recording both the spoken word and behaviour it is a busy half-hour Minimal direction is given because so often the apparently irrelevant may be highly significant Moreover—and how many of us are ever taught this as students?—obvious omissions, evasions, and contradictions should be recorded If in history-taking one is repeatedly frustrated in trying to obtain consistent information about one particular topic—e g, the pregnancy or the feeding situation—it will afford little, to press harder for an answer, and nothing at all if the questioner is by now exasperated Of course, a certain degree of orderliness is essential in the gathering of a history, but this is not in any way incompatible with a non-directive technique

Essential in the interviewer is a sympathetic attentive listening attitude There is here a special difficulty for the contemporary physician All his training from undergraduate years onward has groomed him for a role of action He is expected to make decisions, to advise, to prescribe Now, disconcertingly, he is required to adopt ah essentially passive role In the face, perhaps, of a singularly unmanageable child and completely ineffectual mother he must remain not only a passive observer but also a relaxed one Some can never hope to achieve this, but for the majority the most effective aid is determined concentration on the task of recording what is happening The physician must listen sympathetically without judging, criticising, advising, or becoming emotional himself, but giving his full attention Even a very little proficiency in the technique of the psychotherapist (for that is what is being described) will expose the interviewer to an even trickier hazard—the attitude of the parent towards him

The physician may be surprised to discover that the adoption of these few modifications in interviewing technique often produces a rather startling response, and by no means invariably a friendly one Whether the parent's response is one of dependency, gratitude, hostility, or rivalry, it will almost invariably appear so exaggerated in intensity as to seem inappropriate to the clinical situation An explanation of these transference phenomena is not within the scope of this paper, but their understanding is important and can be achieved only by discussion of the cases with a trained psychotherapist And still the physician must remain interested, sympathetic, and undismayed

A first interview emotionally charged in this way should invariably end with the offer of a second appointment, which may develop into a series of interviews To the distraught parents this is the concrete evidence that here is a doctor who accepts them, “ badness and all ” A first interview held jointly with both parents and child is of such rich potential that it is surprising how methodically many child-guidance clinics eschew its use It must be very seldom indeed that a child hears in a consultation anything said about itself which is half as frightening as it has already constructed in its own imagination

Ætiology

There can be little doubt that events in pregnancy can contribute to later distortions of the mother-child relationship (Caplan 1951) We are all aware of superstitions and old wives' tales connected with pregnancy, and any one of these is a potential source of danger to an expectant mother Curiously, these appear to operate universally, irrespective of intelligence, education, or social class Each culture has its own favoured beliefs, but none is free I do not suggest that, because an expectant mother has had mixed feelings about a pregnancy or has worried a great deal about some thought or action, a disturbed mother-child relationship must inevitably follow This happens only when the event becomes coloured with guilt It is almost certainly true that the core of the disturbance really belongs to a much earlier point in the mother's emotional development, and that this is “ triggered off ” by a psychic event during the pregnancy

A boy, aged 2½, had violent temper outbursts on the mildest provocation As a baby he cried all the time, and brought up his bottles His brother, ten months older, was well The mother spontaneously described the circumstances of her father's death which occurred during the early months of the pregnancy He was in hospital and she was asked to take him to her home Instead, she persuaded another relative to do this, did not tell the truth about his condition, and he died within a week The baby was unwanted, and she tried to prevail on her doctor to bring about an abortion From the start this mother saw the child as a “ monster ” who would grow up to revenge himself on her for her death wishes against him He cried almost continually throughout his infancy and she has described how she would hurl him into the bed screaming that he should never have been born The battle between mother and child had raged for practically the whole of his short life What we observe here is an event in pregnancy leading to a distortion in the mother's perception of her infant son It is understandable that she could be neither loving nor protective towards an avenging monster The improvement in the mother-child relationship and in the behaviour problem during the ten weeks' treatment was quite dramatic It was remarkable to contrast the original picture with the affectionate competent mother of a few weeks later

Yet another crucial epoch is the time of the delivery Of the greatest importance here is the reaction of the mother's near relations, especially of her own mother, and of her husband The fact that at this stage the father's role vis-à-vis the child is indirect does not mean that it is unimportant. In many eastern countries the birth of a daughter is still regarded as something of a tragedy, and husband and relations may make no secret of their disappointment Such crudity is not part of our western culture, but that is not to say that we have not our own pitfalls In some respects our highly organised obstetric routines may contribute to maternal anxiety

A mother may by chance be kept waiting a considerable time after delivery before having the infant brought to her There can hardly be a woman who, in these circumstances, does not rapidly become convinced that something is amiss with the child As she lies in anxious dread, self-accusation begins, and all the trivia of pregnancy assume immense proportions Both rational and irrational factors may play their part In recalling the events connected with a child's birth it is remarkable how often these mothers describe the midwife or the ward sister as a heartless tyrannical figure against whom the strongest feelings of fear and hate were harboured It is clear that in the great majority of instances there is no substance in these assertions, and that the conviction with which they are held is clear evidence of neurotic distortion The failure of doctors and nurses to understand this sort of mechanism can cause them to contribute unwittingly to these irrational attitudes, and this may have repercussions not only on the course of the labour but also on the mother's handling of the child

In certain circumstances the disturbed relationship is activated by the child

An infant may be born with a disfiguring congenital abnormality—e g , hare-lip It is very rare for the mother outwardly to reject such a child, but it is common for her to make this child the centre of her whole menage, sometimes to the neglect of her family, and, as it grows, to develop a pathologically overprotective attitude Personality disturbance associated with congenital abnormality is a subject ripe for investigation and may well be preventable in the first weeks or months of the child's life

Another, though much less obvious, example of the same kind of sequence of events is when the baby is extremely unresponsive This may happen before it is recognised that the child is mentally retarded, or deaf, or destined to show later the clinical picture of infantile autism (Kanner 1943), in which a striking component is disinterest in all human beings In instances such as these the mother is often observed later to be “ cold ” or “ detached ”, and this is invoked as a causal factor This may indeed contribute to a cumulative cycle of disharmony but need not have been the starting-point

Many women can locate precisely a moment at which they suddenly experience the feeling of being a mother—of having a child of their own This may be during pregnancy or at birth but is often delayed thereafter by hours or days Possibly, as in “ imprinting ” in animals (Tinbergen 1953), there are for mother and child critical points at which the relationship “ takes ” If so, it is understandable that separation of mother from child just after birth may have deleterious effects

Under ætiology we must include also the serious psychiatric disorders which may arise at this time—the puerperal psychoses In this event a healthy relationship with the child is impossible, and there is evidence that buried in every such psychosis lie powerful feelings of hatred towards the infant of which the mother is herself unaware In other mothers compulsive thoughts of damaging her child may appear in the early months or years of the child's life, but their roots go deep into the mother's own childhood, and other symptoms of the neurosis have probably preceded the pregnancy Conflicts about femininity which may have remained latent throughout her life may suddenly erupt when she is confronted with the tasks of motherhood, and express themselves as, for example, a profound disgust for breast-feeding The enthusiastic propagandist would do well in such instances to encourage bottle-feeding with scrupulous avoidance of disparagement

It will be seen, therefore, that we are at times confronted with psychotic or neurotic illness However, in many cases of disturbed mother-child relationship the mothers show little or no other evidence of emotional disorder These respond well and often with surprising rapidity to sympathetic interest combined with a reasonable understanding of the type of problem, without necessarily the technical sophistication of the specialist psychotherapist

Conclusion

Every now and again we encounter a mother who is not prepared to cooperate in the treatment or whose capacity for insight is extremely poor What is surprising is that this does not happen more often It is important that those directly concerned with the health of mothers and young children should become practised in the detection of these disorders, this is especially true of family doctors, pædiatricians, physicians, and health visitors in the maternity and child-welfare services Some will, by aptitude and inclination, wish to undertake the management of the cases themselves and should be encouraged to do so It must be emphasised, however, that success will not be forthcoming without acquiring the necessary technical competence This is probably best achieved by regular case conferences under the supervision of a child psychiatrist, who must also be available to take over the occasional case demanding expert intervention

Only by careful follow-up studies can the long-term effects of this form of treatment be assessed, but there are enough data to make us cautiously optimistic Already there can be no doubt that this work provides a field for interesting and potentially important research

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ARTIFICIAL INSEMINATION

By a Practitioner

Amid the emotion, confused thinking, and uninformed opinion that surrounds the subject of artificial insemination by donors, it is perhaps legitimate to inquire why this procedure is ever contemplated and in how many families it is now used

Setting aside situations in which it would in no circumstances be considered by a doctor, what kinds of case remain as possibly suitable for AID and why?

The number of couples seeking this method of treatment is small and will always be so No couple would wish to have a child by artificial means if they could have one naturally The demand for AID is also limited by the fact that of the 8–9% of married couples who are subfertile, in only 1 in 10 is the husband irremediably sterile Fears that AID might become widespread are therefore groundless It is, and must remain, a small factor in the treatment of the barren marriage and a still smaller one in human affairs

It is difficult to estimate accurately the number of children already born as a result of AID One doctor who has practised it for about sixteen years has produced 69 babies by this means, and the total number of doctors using it at present in this country probably does not exceed ten

THE PARENTS

The classical cases are those of the married couple in which the husband has been proved to be irremediably sterile, or of the couple who, having suffered one or more rhesus tragedies, greatly desire to rear a family because they regard it as one of the most, if not the most, important objects of marriage

Such couples may choose AID rather than adoption because the husband prefers to bring up his wife's child rather than an adopted child propagated by two unknown people, and because the wife has the natural desire of every ordinary woman to produce and cherish an infant of her own

Such marriages are stable AID does not attract the frivolously minded couple who take a light view of marriage Husband and wife must have agreed together that AID is the right course for them Neither must have overridden the scruples of the other Neither must think it wrong that spermatozoa from a carefully chosen donor should be used to fertilise the ovum Such couples are, and must be, living a full married life together, which cannot always be said of cases where AIH is employed

The request for AID comes, more often than not, from the husband, who will either approach his general practitioner (not always with success) or make his own, often difficult, search for a doctor who will help him and his wife in this way

The doctor who performs AID must interview both husband and wife and be assured that the request comes from both He must further assure himself that the matter has been properly considered, and that the couple can offer to the child not only a reasonable standard of living but also the love and support that should be every child's heritage The doctor must be satisfied that the couple are mature and sensible—in a word, that they are childworthy

If the request comes through a general practitioner much of this preliminary "screening" will already have been done, for the couple will have been referred for AID only if the family doctor regards them as suitable

If the request comes from the couple, the screening and the final responsibility of deciding whether or not they should be helped in this way falls upon the doctor who is to perform AID

It is not always easy to refuse, but some couples have to be turned down—for example, where one or both are too old or medically unfit, where there is obvious instability and tension, or where one partner has persuaded the other unwillingly into the consulting-room In such cases it is often possible to find infertility factors in the wife, so that the doctor can advise against AID on that score as well as explaining the other difficulties

The responsibility, though a heavy and anxious one, is no more onerous than that assumed by those who arrange adoptions Indeed, in some ways, the chances of making mistakes are fewer, for an AID child will at least be reared by its own mother The handing out of a child, however engendered, to any couple who ask for one is a big responsibility, but experience suggests that it is more likely to go right with AID than with adoption

No doctor in his senses would try to persuade a couple to accept AID as a solution to their barrenness against their own judgment, religious beliefs, or ethical code Nor would he agree to use AID without the knowledge and willing consent of the husband

The manner in which a child is conceived is surely the parents' private concern provided that they deal fairly with their A.I.D. child (and experience shows that they do) and provided that, by having such a child, they do not defraud some other member of the family of a lawful inheritance without agreement. Such family agreements are made and will probably become more common. For example, the parents of a sterile son with a farm to hand on, which would have been sold if he had had no children, strongly advised him to allow his wife to receive A.I.D. These children have brought great happiness to the whole family, particularly to the grandparents.

There seems to be no point in informing the child, at any stage of its growth, that it is a "test-tube" baby. It is better to let it grow up accepting those who care for it as its parents.

THE OPERATION

Since A.I.D. is not a service that can be properly offered under the National Health Service, and since it involves complicated arrangements, the most suitable place for it to be done is the doctor's consulting-room. The timing of the procedure so as to give the best chance of success is difficult, especially for women who have to travel long distances to see the doctor and can perhaps manage only one visit a month. The correct day in the cycle can be decided only by studying the basal temperature charts, vaginal smears, the characteristics of the cervical mucus, the average length of the patient's menstrual cycles, and so forth.

It is always wise to explain to the couple that normal sexual intercourse should not be restricted during the period that artificial inseminations are being carried out.

The number of attempts needed to achieve pregnancy varies greatly from case to case, ranging from 1 to 4 times per cycle for from one to twenty cycles. The semen used should if possible be not more than three hours old, though success has been achieved with semen considerably older. It is best collected in polyethylene tubes and kept at cool room-temperature.

American workers[1] claim successful results with semen preserved by deep freezing, but their results have not been confirmed in this country.

THE DONORS

One of the most difficult and responsible tasks confronting the doctor who carries out A.I.D. is building up a list of donors. These should be personally known to him, but only in special and rare circumstances to the recipient. It is fundamental that the transaction remain entirely impersonal.

Donors must not only be fertile but also physically and mentally fit. They should be of various types and it is an advantage to have a long list from which to choose. The serological tests of donors must be negative and their blood-groups ascertained. They are used more or less in rotation, but some attempt is made to match the skills and aptitudes of the donor with that of the husband. A donor may be called upon from twice to twenty times a year.

Experience shows that, though couples may show interest in the physical and mental characteristics of the donor, once a child is conceived and born no further reference is made to him, unless another child is desired, when parents almost always ask for the same donor.

Donors should preferably be sought among married men with families of their own who donate with their wives' knowledge and consent, and without fee. The all too common gibes that donors must regard themselves as supermen or, alternatively, that they are irresponsible persons who donate for gain and without regard for the destiny of their seed are unfounded. Men of the right calibre will not donate unless they can trust the doctor responsible and can feel assured that their help is given only to childworthy couples.

THE CHILDREN

The bogy of intermarriage between half-brothers and half-sisters has been much exaggerated: the risk is certainly less than that of marriage between adopted or illegitimate sibs. The number of illegitimate births per annum is over 50,000 and of adoptions about 15,000, whereas an outside estimate of the annual number of A.I.D. births is 500. Though the donors may be drawn from a limited area, this is not true of the recipients, who come from far and wide.

A register of A.I.D. births, which would be open to inspection under proper safeguards by authorised persons, would put many minds at rest, but whether a satisfactory system could be devised can be decided only by those with expert knowledge of the legal and administrative intricacies of registration. It is, however, important that doctors practising A.I.D. should keep careful clinical records of every case, and, until enough information has been collected to answer more fully the questions in so many thoughtful minds, every effort should be made to keep in close touch with A.I.D. families.

In a series of more than 70 cases only 2 have been lost sight of, and nearly a third of them have returned for further A.I.D. In all there were 93 pregnancies in 70 women (69 live births, 4 stillbirths, 14 miscarriages, and 6 still in utero). The children born are satisfactory both physically and mentally. Though the children have a resemblance to the donor they tend to resemble more nearly their mothers and "fathers"—partly no doubt because they absorb their habits and facial expressions. The families have developed as a harmonious whole. So far no congenital defects have come to light. These A.I.D. families form only a small part of a much larger series of infertile couples investigated and treated, and since all cases are followed up there is no reason why A.I.D. families should feel conspicuous.

NATIONAL VARICOSE FOUNDATION

In July, 1956, the National Varicose Foundation was established and given four aims:

(1) To sponsor the building and maintenance of an independent varicose clinic, to be staffed by a team of specialists who could train and encourage others to take a deep interest in varicose veins and their treatment.

(2) To provide funds (*a*) to expand the present facilities at hospitals and clinics in Great Britain, and (*b*) to support clinical and scientific research at these and other centres.

(3) To explain to sufferers the underlying cause of their condition and so help them towards prevention, alleviation, and cure.

(4) To convince the authorities of the need for specialist-staffed varicose clinics and to help and advise, if requested, on the setting up of these within the framework of the National Health Service.

At a reception in London on May 15, Dr. STANLEY RIVLIN, chairman of the Foundation, spoke of the five million people in Great Britain with varicose veins and the half-million of them whose legs were ulcerated. The problem was gigantic, but it was the best of lost causes, for it was one that could be rescued. The present focus of the Foundation's aims was the erection of a specialist unit for outpatient and inpatient treatment and for research. A building fund has been set up from which it is hoped that a substantial new unit will emerge. Plans have already been prepared for this new London Varicose Clinic, which will contain an outpatient department, an inpatient department with 32 ward beds and 8 single rooms, a twin operating suite, a research department, and a lecture hall.

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[1] Bunge, R. G., Keettel, W. C., Sherman, J. K. *Fertility and Sterility*, 1954, 5, 520.

The design of the outpatient department was based on experience gained in the present London Varicose Clinic at Battersea. Patients under treatment are dealt with together in one large room, where leg bandages are removed, and where patients sit talking until they are called in groups of 4 or 6 for treatment in a separate room. The inpatient department had been divided into 4 wards, each of 8 beds. The beds would normally be used for the treatment of varicose veins, for the treatment of ulcerated legs was ambulatory. Postoperative treatment of varicose veins included walking for five minutes every two hours, on the first and second postoperative day. Corridors had therefore been made wide to allow room for ambulatory inpatient traffic.

The twin operating suite consisted of a series of concrete "bubbles" intercommunicating to permit a "conveyor-belt" system of operating. A thorough operation on one leg by a single surgeon often took up to 1½ hours, and it was proposed to have a surgical team, the senior member to carry out only the vital part of the operation—the juxtafemoral ligation or juxta popliteal ligation. His first assistant then continued with the phlebectomy, and the second assistant did the sewing up and bandaging. It should thus be possible for one team to operate successfully and thoroughly on four cases a session, instead of the normal two.

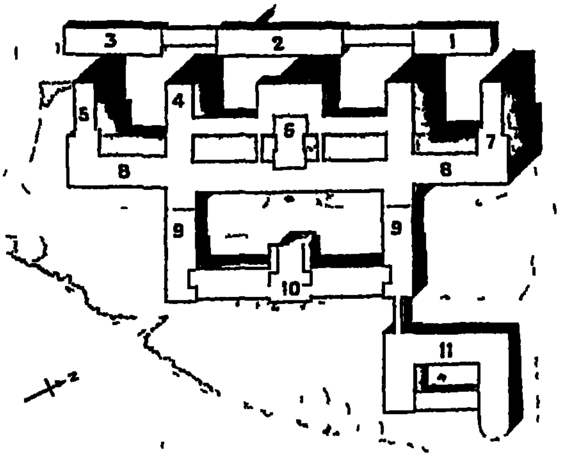
The unit was designed by Denis Clarke Hall, F.R.I.B.A., in association with Robin de Beaumont, A.R.I.B.A., honorary architect to the Foundation.

At the reception, Sir ARTHUR PORRITT wished the venture well, and guests were able to inspect a model of the proposed new clinic, which is estimated to need about £400,000 for its completion.

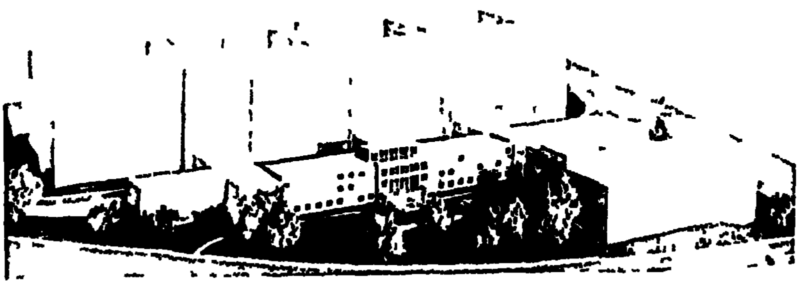
SHEFFIELD'S NEW TEACHING HOSPITAL

ON May 17, Queen Elizabeth, the Queen Mother, laid the foundation of the teaching hospital which is to be built on a site about a mile from the centre of Sheffield.

Plans for the new hospital were first discussed over thirty years ago. Shortly before the late war an appeal was launched to build it, and the trustees still hold a considerable sum of money collected at that time. An architectural competition was also held, which was won by the architects of the present building, Messrs Adams, Holden, and Pearson. But the war and post-war difficulties prevented building and it was not till 1953 that it proved possible to open the Charles Clifford Dental Hospital which was part of the original plan and which stands on an adjacent site.



1 Laundry
2 Boiler-house
3 Works department
4 Professorial unit
5 Staff-nurses' hostel
6 Main kitchen
7 R.M.O.s' hostel
8 Ward blocks
9 Polyclinic phase 2
10 Polyclinic phase 1
11 Medical sciences block



The new hospital when it is complete will be a comprehensive acute general hospital with 800 beds. It will of course be closely associated with Sheffield University, and it is ideally situated to form a hospital/university campus. It is also readily accessible to patients and visitors. It stands on some ten acres of land, and advantage has been taken of the sloping site to form interesting groupings of buildings and yet allow easy and convenient communication between them. At the highest level, at the back of the site, will be gathered the various service departments with a self-contained area for the delivery of goods. The inpatient block will be in the middle of the site with a through road to it. The outpatient and the laboratory block will be at the lower level and will also have its own road. The two blocks will be linked by corridors. The whole building is to be constructed in vertical blocks so that the planned extensions may be made horizontally.

When the outpatient department is completed it is hoped to go on as soon as may be with the next stage, which will provide 52 beds for inpatients, and then to continue the building programme steadily until the whole hospital is complete.

Occasional Survey

THE CONTRIBUTIONS OF SURGERY TO THE TREATMENT AND UNDERSTANDING OF PARKINSONISM

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ALL methods of surgical attack in Parkinson's disease and postencephalitic parkinsonism aim at relief of symptoms No operation eradicates either of these diseases or arrests their evolution Tremor, often the most obvious manifestation, has claimed most attention from the neurosurgeons, but although it is the commonest early symptom and is present in variable amplitude in most patients with advanced parkinsonism it is far from being the chief presenting symptom when patients seek surgical treatment. Most patients then complain of disability, despite adequate muscular power there are slowness and poverty of movement. Some patients do, however, ask for relief from tremor, either because it embarrasses them or because it interferes with function

OPERATIONS

The operations will not be discussed in the order in which they were introduced but in an anatomical sequence which throws light on the route followed by the abnormal nervous impulses in the Parkinson syndrome

Operations directed at Globus Pallidus

While attempting partial section of one cerebral peduncle for contralateral tremor Cooper inadvertently damaged the anterior choroidal artery (fig 1) and was obliged to coagulate it. Pedunculotomy was then abandoned, but the patient was freed from tremor on the opposite side, although there was no hemiplegia and there were no other abnormal neurological signs which, according to the anatomical work of Abbie (1933), were to be expected

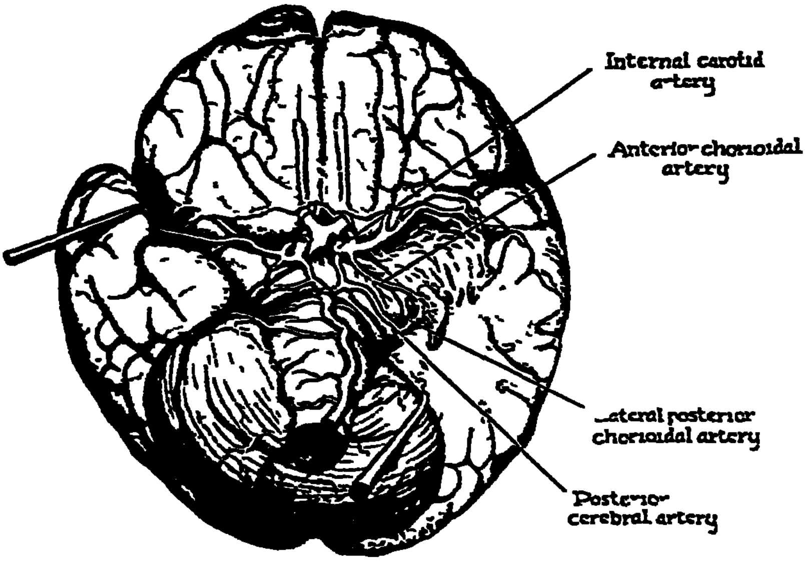
Internal carotid artery
Anterior choroidal artery
Lateral posterior choroidal artery
Posterior cerebral artery

Fig 1—Part of left temporal lobe has been removed to expose anterior choroidal artery By courtesy of Carpenter, Noback, and Moss (1954) and the Editor of *Archives of Neurology and Psychiatry*

As a result of this experience Cooper (1953) continued to coagulate the anterior choroidal artery for Parkinson's disease after angiography to demonstrate the artery and any variation of its origin It usually arises from the internal carotid artery just above the posterior communicating artery (fig 1) This operation relieved contralateral tremor in 55 patients

Although Abbie (1933) showed that many important structures could be stained by injecting dye into the anterior choroidal artery, Mettler et al (1954) showed that bilateral coagulation of the artery in the chimpanzee produced infarction of only a small part of each globus pallidus

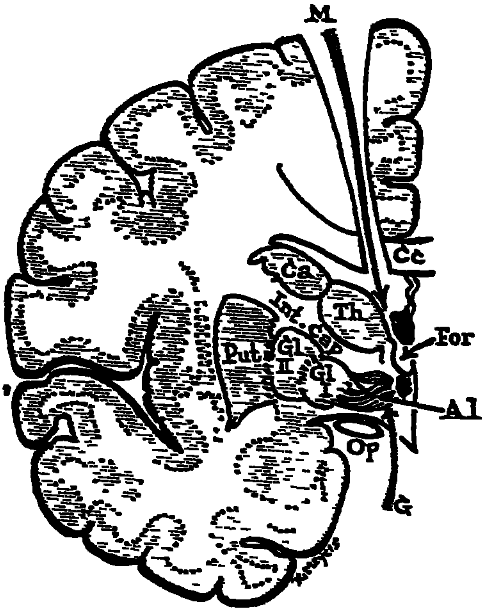

Fig 2—Russell Meyers diagram. A1, pallidofugal fibres (upper bundle is fasciculus lenticularis and lower bundle is ansa lenticularis) M, Meyers original transventricular approach to these fibres, G, Guiot's approach Ca, caudate nucleus, Th thalamus, Put, putamen Gl. I, medial segment of globus pallidus, and Gl. II, lateral segment of globus pallidus

Carpenter et al (1950) produced choreiform movements in monkeys by partially destroying the subthalamic nucleus and either reduced or eliminated these movements by partially destroying the contralateral globus pallidus These experiments were subsequently checked histologically

Coagulation of the anterior choroidal artery carries at least a 10% mortality and, despite the optimism of its originator, sometimes causes severe contralateral hemiplegia and other serious neurological complications This operation is therefore now rarely done having given place to less risky methods of destroying the globus pallidus—e g , injection of procaine in oil (Narabayashi and Okuma 1953), injection of alcohol (Cooper and Poloukhine 1955), implantation of radioactive isotopes (J B Campbell, personal communication), and mechanical means (Obrador 1957)

The most popular of these methods is injection of alcohol (chemopallidectomy) through a burr-hole, orientation being obtained by pneumoencephalography The mortality in 245 cases was 2·8%, and postoperative hemiplegia developed in

2% of patients, relief of tremor and rigidity was obtained in 70% (Cooper 1956)

Our knowledge of the role of the globus pallidus in the mechanism of parkinsonism is derived from the pioneering work of Meyers (1940, 1942), who tried several operations directed at the basal ganglia, but the most effective is section of the pallidofugal fibres—the ansa lenticularis and the fasciculus lenticularis (fig 2) Originally these fibres were cut through the lateral wall of the third ventricle approached through the frontal lobe and the anterior horn of the lateral ventricle Meyers (personal communication) reported the results of 22 such operations as follows

	No of patients
Much improved (tremor-free, some rigidity persisting, no neurological deficits due to surgery)	8
Improved (tremor and rigidity reduced but not abolished, or, if abolished, attended by some degree of post-operative dyspraxia, paresis, or spasticitv)	10
Unimproved	2
Operative mortality	2

Patients were followed up for at least 18 months and at most 13½ years

Meyers (personal communication) has abolished tremor and rigidity in 3 patients by subjecting the ansa lenticularis to irradiation by multibeam ultrasonic waves

Other workers claim good results from division of the pallidofugal fibres by other methods (Fénelon 1952, 1953, Guiot and Brion 1953, Spiegel and Wycis 1954)

Operations on Cortical Projection Areas

Horsley (1909) was the first to operate on the frontal cortex for involuntary movements He showed that removal of the precentral gyrus, area 4 of Brodmann, abolishes contralateral athetosis Bucy (1948, 1951) has also excised the precentral cortex for choreo-athetosis and for tremor The involuntary movements were eliminated at the expense of spastic paralysis of the affected limbs

Ward et al (1948) produced alternating tremor at rest in monkeys by electrocoagulation of parts of the reticular formation of the midbrain, and temporarily eliminated the tremor by excision of the motor and premotor cortex (Brodmann's areas 4 and 6)

Operations on Non-pyramidal Corticofugal Fibres

One of the operations tried by Meyers (1942) was section of the anterior limb of the internal capsule approached through the anterior horn of the lateral ventricle and exposed by removal of the head of the caudate nucleus After this operation there are transitory hemiparesis and persistent reduction of amplitude of the tremor

Pedunculotomy

Division of the lateral two-thirds of one cerebral peduncle for contralateral involuntary movements was first done by Walker (1949) In this operation both pyramidal and non-pyramidal fibres are divided There is diminution or elimination of tremor, but severe hemiplegia results

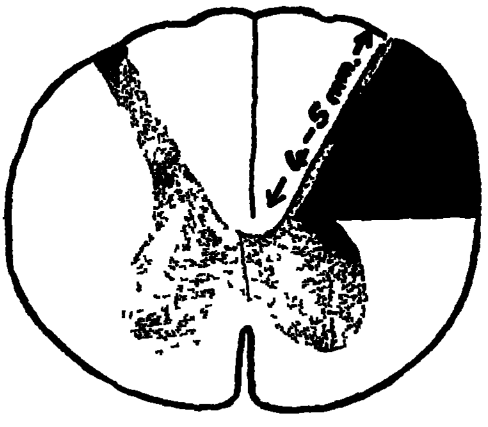

Fig 3—Putnam's (1940) chordotomy

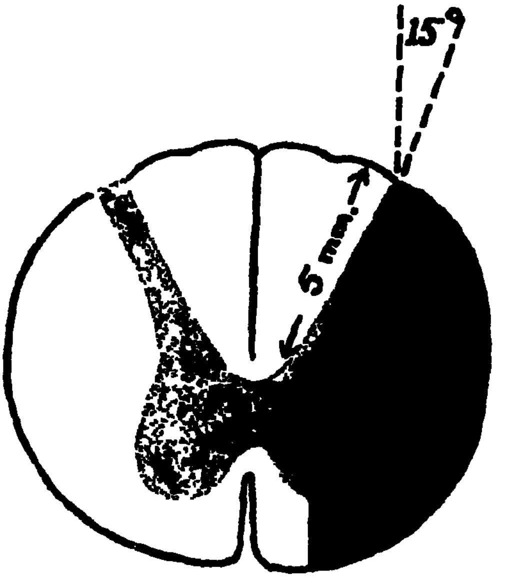

Fig 4—Complete section of lateral column

Operations on Spinal Tracts

One of the patients whose record appears in James Parkinson's (1817) monograph had a cerebral hæmorrhage and immediately lost the tremor on the hemiplegic side This fact, together with the observation that section of the pyramidal tract in monkeys causes little or no lasting disability, led Putnam (1940) to divide the crossed pyramidal tract unilaterally at the second cervical level for unilateral tremor (fig 3) There was reduction of tremor in 15 of 22 patients, and most of the patients completely recovered from the post-operative hemiplegia After this operation complete relief of tremor is not obtained, the tremor tends to return to its former amplitude (Oliver 1953) Unilateral tremor can, however, be entirely eliminated by complete section of the lateral column of the cervical part of the spinal cord (Oliver 1950) (fig 4)

Operations on any part of the pyramidal system should only be done on patients who have had hemiparkinsonism for at least five years without the slightest evidence of involvement of the other side The price of elimination of tremor by complete section of the lateral column is permanent hemiparesis and contralateral analgesia and thermanæsthesia of variable level but usually reaching the inner border of the arm Of 20 patients 18 were entirely relieved of tremor and 2 were only partially relieved Other workers have confirmed the results of this operation (Sjöqvist 1954, Gaches et al 1955)

DISCUSSION

Pallidectomy is the most promising advance in the treatment of parkinsonism and the most generally applicable operation It can be used both in unilateral and in bilateral parkinsonism, in the latter one side is done first and the other after an interval of at least three months This operation has a more lasting beneficial effect on rigidity and motor function than on tremor In long-standing unilateral parkinsonism in which tremor is the presenting symptom, either because it is embarrassing to the patient or because it is sufficiently severe to interfere with function, section of the lateral column is the more effective operation, but nevertheless unilateral pallidectomy should be tried first in such cases, because the patient may be satisfied with this, and damage to the pyramidal system is usually avoided.

The neuronal degeneration found in parkinsonism cannot be better defined than by quoting Greenfield and Bosanquet (1953)

> " examination has shown the lesions in the basal ganglia in our cases of idiopathic Parkinsonism to be slight by comparison with those in the brain-stem, and to differ in no respect from those found in many senile and presenile brains from cases with no symptoms of Parkinsonism. In post-encephalitic cases the lesions in the basal ganglia are often more definite, but in them also they are much slighter than those in the substantia nigra There is general agreement that in post-encephalitic Parkinsonism the *substantia nigra* is severely damaged and in some cases is reduced to a glial scar in which very few pigmented cells can be seen. In idiopathic paralysis agitans the lesions in the substantia nigra although usually less severe than in post-encephalitic cases, are always very evident when the various cell groups in this nucleus are compared with the normal "

In parkinsonism the affected neurons are in various stages of degeneration Brain-stem tumours and infarcts which completely blot out these cells do not produce parkinsonism, which therefore results from abnormally discharging neurons rather than from a release mechanism.

Electrolytic lesions of the reticular formation of the mid brain in monkeys cause tremor, and these lesions are composed of a zone of destruction surrounded by a zone of *degeneration*

It is suggested that the neurons of the substantia nigra —pars compacta or central portion (Mettler 1948)—send abnormal impulses to the globus pallidus in the strionigral tract, now recognised as an ascending pathway, although its name suggests that it is a descending tract (Keller and Harris 1941, Mettler 1943, 1944, 1945a and b, Ranson and Ranson 1942) The abnormal discharges leave the pallidum in the pallidofugal fibres (ansa lenticularis and fasciculus lenticularis), some of which are known to enter the ventrolateral nucleus of the thalamus (Rasmussen 1945) (It will be recalled that destruction of the globus pallidus or of the pallidofugal fibres diminishes or abolishes contralateral parkinsonism) The disordered impulses presumably then pass from the thalamus to the motor cortex and thence along the pyramidal or intimately related fibres, because excision of the motor cortex, pedunculotomy, or lateral-column section abolishes tremor The abnormal impulses are finally fed into the anterior-horn cells and thus interfere with muscular tone and function Sensory pathways seem to play but a passive role, because neither division of sensory nerve-roots of affected limbs (Pollock and Davis 1930) nor division of the posterior columns of the spinal cord in the cervical region (Putnam and Herz 1950) has any effect on parkinsonism

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NUTRITION AND HEALTH IN THE WEST INDIES

THE third annual meeting organised by the Standing Advisory Committee for Medical Research in the British Caribbean was held at the University College of the West Indies on April 12 and 13, under the chairmanship of Prof A C. FRAZER (Birmingham) and Sir GEORGE PICKERING (Oxford) Food in relation to health and disease was the theme.

Agriculture

Dr H. C. MILLER, director of the Jamaican Department of Agriculture. emphasised the need for increased agricultural production in underdeveloped countries Three-quarters of the land in Jamaica was mountainous, and there was available for production only [illegible] of an acre per head of the population In addition [illegible] of the 200,000 farms were under 10 acres Thus scientific farming or even the introduction of improved methods was time-consuming

Dr G GIGLIOLI (British Guiana) said that two-thirds of the workers on the sugar estates in British Guiana have been rehoused and provided with their own plot of land for vegetable production and poultry rearing Many families could produce more than enough for their own needs Malaria eradication had resulted in considerable improvement in nutrition.

Nutrition Surveys

A pilot nutrition survey of five low-income areas in Jamaica was reported by Dr K STANDARD, of the Government Nutrition Research Team The incidence and distribution of dental caries was shown to be related to the fluorine content of the drinking-water The children were thin and underweight according to British and American standards

Elementary-school children in British Guiana had been studied by Dr C C. NICHOLSON in 1950, 1951, 1952, and 1958 Since 1954 a snack meal consisting of skimmed milk, food-yeast-enriched biscuits, and fish-liver-oil capsules had been distributed to the schools In the 1958 survey the effect of this was apparent. There had been a remarkable improvement in health, but there were still some skin, eye, and mouth lesions that might indicate slight residual vitamin A and B deficiency

The value of milk supplements was also stressed by Dr L. HARNEY (St. Kitts), who pointed out that there had been a significant drop in infant mortality, compared with the " pre-milk era ", which did not appear to be due to other causes

The failure of vitamin B_{12} and aureomycin supplementation to influence the growth of protein-deficient Jamaican children was reported by Prof I F S MACKAY (U C W I)

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Veno-occlusive Disease

Experimental production of veno-occlusive disease of the liver in calves was described by Prof G **Bras** (U C W I) and Dr D M **Berry** (Jamaica) *Crotalaria fulva* was the toxic plant The condition appeared to be closely similar histopathologically to that in man

Mayaro Virus

Dr W G **Downs** (Trinidad Regional Virus Laboratory) reported on the immunity to Mayaro virus found in the inhabitants of several West Indian territories It was confined to British Guiana and South-East Trinidad

Malnutrition

Malnutrition in infants was discussed by Dr B E R **Symonds** (Trinidad) In 69% of children who died between the ages of 1 month and 1 year, malnutrition was the sole or major contributory cause This was considered to be mainly due to ignorance or apathy on the part of the mother

Kwashiorkor

10 patients with kwashiorkor who had recovered were reviewed three and a half to five years later by Dr E H **Back** and Professor **Bras** All were well, 5 were below normal height and weight for their age, 4 had hepatic enlargement All the livers were histologically normal, including 1 that had shown fibrosis several years previously

Megaloblastic Anæmia

Nutritional megaloblastic anæmia in children about 1 year of age was reported by Dr J E **MacIver** and Dr E H **Back** (U C W I) This had been noted in 50 children over a two-year period—26% of all cases of malnutrition under the age of 2 years In these patients the hæmoglobin was less than in the usual cases of malnutrition, being 7 g per 100 ml or less All cases responded dramatically to the oral administration of folic acid 10 mg a day

Plasma-protein Levels

A paper by Dr B B G **Nehaul** (British Guiana) showed that in a group of East Indian patients the plasma-albumin level was lower and the plasma-globulin level higher than might be expected in a comparable series in Britain or America

Feeding Experiments

Mr C **Mendes** (M R C) showed that in weanling rats fed on a low-protein, high-carbohydrate diet growth was arrested and muscle-protein was considerably reduced—a situation similar to that observed in the protein depletion in the infant On refeeding there was a lag period before the synthesis of new tissue reached a maximum rate

Incidence of Cardiovascular Disorders

The low incidence of myocardial infarction in the Jamaican patient was pointed out by Dr J A **Tulloch** (U C W I)

The high incidence of aortic atherosclerosis in the Jamaican was demonstrated by Dr W B **Robertson** (U C W I) The findings were comparable to those observed in New Orleans On the other hand myocardial infarction appeared to be relatively uncommon, approximating more closely to the incidence in Guatemala

Placental Changes

Dr W B **Robertson** and Dr H G **Dixon** (U C W I) reported a combined clinical and pathological study of the maternal blood-vessels at the placental site in normotensive and hypertensive pregnancies in women undergoing cæsarean section Distinct changes in the vessels were noted in pre-eclampsia and in essential hypertension Intimal proliferation or swelling with considerable reduction in the lumen or sometimes complete occlusion of the lumen was found in the muscular and decidual vessels in the eclamptic or hypertensive woman

Adrenal Glands

The adrenal gland was shown to be notably smaller in the Jamaican patient than in the British subject by Dr G **Stirling** (U C W I) This change involved only the cortex and it was particularly distinct in children

In England Now

A Running Commentary by Peripatetic Correspondents

The importunate assimilators of reprints provide problems for impecuniary authors who do not work in university departments which usually pay both for reprints and for their postage Shall the author limit himself to the number of reprints given him by the editor and shall he send them, as some scientists do, only to those whom he knows to be working in the same field? If more reprints are to be purchased (and at a rising cost), how is he to forecast the popularity of his latest masterpiece? Will 200 meet the demands of these insatiable addicts? And if one's secretary says firmly, " No, 50 will do," how then to judge priorities when the postcards flow in like a river in spate?

If the principle of first-come first-served is accepted, then the few courteous Englishmen who wrote you a pleasantly phrased letter will soon be outnumbered by the senders of the stereotyped postcards (with a printed signature) from North America Then even the nice American from Baltimore, who gave you and your wife too many rocks on the rye last summer, and who scrawls " Love to Linda " (her name is Lucy) on his postcard, will be disappointed Rejected, too, will be that splendid solitary specimen of the anglophil Frenchman, the only physician in France who can understand what you have written Forgotten, also, will be that delightful South African —one of the few who replied in gratitude last year, having received an earlier and signal mark of your favour Omitted, too, would be those doctors behind the Iron Curtain, in Hungary and Rumania for example, towards whom one would be honoured to make so trivial a gesture of fraternity Rebuffed also the darling physician from Bucharest, who sent a postcard picturing the theatre at Cluj, and on the postage-stamp a portrait in sepia of Eminescu—a brilliant impression like an 18th-century mezzotint And, even more regrettable, to have left unsatisfied the redoubtable Latinist from East Berlin who wrote

> Honoratissimus Dr X
>
> Ista labor multum mea interest, quoniam similis investigationes perfero Oro, mittatis ad me supra dictum separatum atque alia separata similis generis
>
> *Manganese Deficiency in Cerebral Disorder*
>
> In publico propositum est Lancet I, Volume MCMLVIII, pagina DLXIII Multas gratias habete
>
> Vale

Or would you wish, Mr Editor, that I should enhance the circulation of *The Lancet* by refusing the requests of all these obsessional collectors, believing, as you and I do, that *The Lancet* is a journal to be bought and not merely to be read?

* * *

The parish church of Wirksworth, Derbyshire, is known for its beauty and even magnificence, and it is one of the oldest foundations in England, for a church certainly stood there in the 7th century There are many monuments in it to members of ancient local families—Lowe of Alderwasley, Blackwall of Blackwall, and Gell of Hopton—but there is also a simple mural tablet behind the pulpit which reads

IN MEMORY OF
WILLIAM WEBB, M D , F R C S , J P
DIED 27TH AUGUST, 1890,
Aged 59

I had often wondered how this highly qualified doctor came to have a memorial in this charming but tiny little country town So I looked up what the journals of the day had had to say about him, and he appears as indeed a man of parts He was in practice in Wirksworth for over twenty years and seems to have just about run the place

"Dr Webb was earnest and thorough in everything that he undertook, whether it was in politics in which he took an active interest or in the promotion of the sanitary improvement of Wirksworth which he sedulously advocated or in pleading the cause of the Cottage Hospital of which he was, from its foundation, the Medical Officer and active supporter "

One can imagine the enthusiasm with which this man of drive and initiative got the cottage hospital going at last somewhere in which the new Listerian surgery could be practised in a proper manner

But his health obliged Dr Webb to retire early from practice, and it is not perhaps too wide of the mark to hazard the guess that when he did so, his partner felt the need of a successor with surgical ability At any rate, in 1877 there came to Wirksworth none other than Frederick Treves True, he soon went back to London and to fame, whereas Webb's reputation remained local But I feel that this Wirksworth surgeon deserved his modest immortality in stone at least as much as the 16th-century grandees lying in their sculptured tombs in the chancel

* * *

Would you agree that the average English-male/American-female city-dweller has a tailored look, as if he/she had been poured into his/her suit? That he/she has every hair neat and slicked down as if he/she had just come from the barber's/hairdresser? And that he/she generally wears cuff-links/costume-jewellery and a set expression? While the average English-female/American-male city-dweller has a more casual look, as if she/he had bought her/his suit off the peg? That she/he has a more elemental hair-do, as if she/he had done it her/himself? And that she/he is inclined to wear rubber-soles/galoshes and a breezy expression?

* * *

The rugger type on the Holborn escalator nearly knocked me over in his rush But he found time to glare over his shoulder Now I can understand that he was in a hurry and had to push me out of his way, but what I can't understand is why he should bear me a grudge for it There is a lot of psychopathology to be explored on London's underground in the rush hour

* * *

A luxurious bank has been opened on the south side of Piccadilly Circus It is intended primarily for overseas visitors and was lately described in an evening newspaper as follows "The doors are of silver bronze bordered with red marble quarried from Oran, the source once used by the Romans for the Pantheon The close-carpeted interior has deep armchairs for customers"

What a contrast to the hospital scene 1958, where too often highly trained and qualified doctors, nurses, medical auxiliaries, are carrying out complex modern treatments in old buildings with out-of-date annexes, poor equipment, and overcrowded casualty and outpatient departments The general standard of hospital decoration and hygienic cleanliness is related, not to medical needs, but to a "pruned" hospital budget. How unfortunately the hospital, which is in continuous action 24 hours a day, compares with the bank How wonderful it would be if banks and other prosperous business concerns could be induced to sponsor and help the hospital capital development plans so that doctors will no longer be ashamed of the premises on which they work

* * *

"I had a pain in the mid watch," said the patient (from Portsmouth)

"Where's that?" asked the house-surgeon (from Pakistan)

"It's not where, it's when He means he felt it in the early hours—about pit-time," explained the staff-nurse (from the West Riding)

* * *

At Brightsea did the Councillors
A stately pleasure ground decree
Where through a pipe not far away
Town sewage bubbled on its way
Down to a sunlit sea

"A sewerage plant might there be placed,"
The M O H had shyly said
"What does the fellow contemplate?
The scheme would cost a five-bob rate,
Chap must be off his head!"

Letters to the Editor

THE ROYAL COMMISSION AND RESTORATION OF GENERAL PRACTICE

SIR,—Mr Wilfrid Adams, in his letter of May 10, makes some outstanding points on which I hope you will allow me to comment

"A successful outcome of the work of the Royal Commission depends on radical upgrading of conditions in general practice" At present what incentive is there to encourage good work or good conditions when the doctor who runs a first-class practice from first-class premises with all necessary ancillary help does not get paid one penny more than the doctor who practises from a lock-up surgery It is only heads that count The worst doctor gets the same money per head Surely now is a wonderful opportunity for the Royal Commission to make recommendations which will get this iniquitous system altered

May I make some suggestions?

(1) *An expense factor*—This would very broadly cover the G P's practice expenses as allowed for income-tax purposes and would directly encourage good work

(2) *Some form of merit award*—This would be given to those doctors who themselves do for their patients all the work for which they have been trained and are competent to do instead of dumping their "time-consuming cases" on the local hospital—a much more expensive procedure

(3) *Awards for higher degrees and diplomas*—It is true that some men find it much more difficult to pass exams than others, but would not membership of the College of General Practitioners show that the holder of this distinction was a man who had given an undertaking to keep himself up to date and to maintain the highest standards of medical practice and who was therefore worthy of recognition?

(4) *A locality allowance* (not to be confused with a mileage allowance)—This would be given to doctors who practise in difficult areas or where a large number of elderly people reside

(5) *Payment for experience*—At present in medical practice the experienced G P is paid exactly the same as his youngest colleague and has to work at top pressure till he retires or dies, whereas in most professions men earn their maximum rewards in late middle life with corresponding slackening of effort This could be achieved in many ways but would probably be most effective if it commenced about 45, rising slowly by yearly increments until age 60, when it would remain stationary until retirement Not only would a G P by this method be able to ease his work by a reduction in his list, without reduction of income, but it would also be a safeguard against any reduction in the ultimate amount of his pension

The all-important time factor

How is it possible, under the present system of remuneration, to give the average general practitioner the time to do his work properly, to give his patients a first-class service, and at the same time allow him opportunity for reading and reflection This point may well be causing thought amongst the members of the Royal Commission, indeed Sir Hugh Watson is reported to have remarked on it

To give a really good service in some 20-odd years of general practice I have found that for morning consultations fatigue begins to set in after about the 15th patient Visits vary according to travelling time, but 12 can be done comfortably, taking interest in each, before the work gets fatiguing This, followed by about 12 patients at night, gives a total of some 40 items of service per day, or a list of about 2500 patients At the present rate of remuneration it is argued that a doctor with a family cannot live and meet his expenses He is therefore forced to take more patients than he would otherwise like to balance his budget

Is it not possible that some of these suggestions could go a long way towards helping the G P to maintain a first-class service without being forced by financial necessity to take on more than he can efficiently manage?

Mr Adams has stressed the material factors just as important in my view are the psychological factors, the sense of bitter frustration, of being treated unfairly, of rankling injustice that is deep in the minds of so many doctors at the present day, which must be eradicated if we are to attract recruits of the right type into the profession

Worthing,
Sussex HAROLD LEESON

MORTALITY FROM CEREBRAL VASCULAR AND CORONARY DISEASE AMONG THE SOUTH AFRICAN BANTU

SIR,—In his stimulating letter of March 8 (p 528), Professor McMichael, referring to coronary-artery disease, states that "others would have us believe that the diet of the Bantu would save us, but the Pietermaritzburg pathologists, Laurie and Woods, think there is as much atheroma in the Bantu as in Barts" As two of those "others", we should be glad to comment on this statement

In the first place, the burden of Professor McMichael's letter relates primarily to *coronary-artery* disease and mortality In their comparison with Barts, Dr Laurie and Dr Woods[1] were referring to *cerebral vascular* disease in the South African Bantu While many believe that the diet of the Bantu is the factor of predominating influence in almost completely protecting them from dying from coronary-artery disease, no-one, to our knowledge, has speculated that their diet has an equal protecting effect against cerebral softening and hæmorrhage In this respect it is interesting to note that countries may differ considerably in the ratio of their mortality from these causes

(1) Mortalities may be high, approximately equally so—e g, England and Wales, Denmark and Sweden[2,3]

(2) Coronary-disease mortality may be low, but that from cerebral lesions high—e g, France, Italy[2,3]

(3) Coronary-disease mortality may be *very* low, yet cerebral disease may be a significant cause of death—e g, among the South African Bantu in Johannesburg, our information indicates that the former mortality is responsible for about 0 6% of deaths, and the latter, 3–4% of deaths[4,5]

(4) Mortality from both diseases may be virtually nil—e g, among Africans in Kampala, Uganda, in Dr Davies' series of 2994 necropsies, coronary-artery disease mortality was 0 03%, that from *cerebral vascular lesions, 0 3%*[6]

But to return to our local Bantu (for whom death certificates are required), it is evident that while mortality from coronary thrombosis presents no problem, this is not the case with cerebral vascular disease[7] It must be stressed, however, that mortality from cerebral vascular disease is still far less than among local white populations

Turning now from the mortality aspect to that of atheroma at this hospital, the proportion of deaths from cerebral softening and hæmorrhage is higher than in Pietermaritzburg, the impression gained, however, is that atherosclerosis of the cerebral vessels appears gross in a smaller proportion of relevant patients than is the case in the series of Laurie and Woods[1] Incidentally, these workers stress "the high prevalence of atherosclerosis and its cerebral complications in Bantu women—contrary to the findings in people of European descent" and quote Dr Lober[8] and the *British Medical Journal*[9] in support If this observation relates specifically to cerebral atherosclerosis and mortality, it is incorrect In the first place, there is a female preponderance of mortality from cerebral lesions in all the countries listed in the relevant World Health Organisation publication[3] More to the point, Dr Lober and the *British Medical Journal* both have in mind *coronary* sclerosis—the word *cerebral* does not even appear

It seems that the pathological lesions in the cerebral vessels of the South African Bantu are compatible with the mortality obtaining On the other hand, according to many observers, the extent of the lesions in the aorta and coronary vessels seem out of proportion to the very low mortality from coronary occlusion

In 1946, in a comprehensive study on Johannesburg Bantu, Becker[10] observed that "in spite of the fact that the coronary vessels are frequently in a diseased condition and the myocardium as frequently damaged, coronary thrombosis is an uncommon lesion" Furthermore, in his letter in your issue of May 10, Professor Becker reiterates that "on occasion" the Bantu develops atherosclerosis as severe as that seen in the local white population In the study of Higginson and Pepler[11] on 523 Johannesburg Bantu necropsies, about 4% showed "severe atherosclerosis of aorta, including ulceration and calcification, but in which atherosclerosis of coronary arteries does not significantly diminish the lumen" at the same time 2% of coronary arteries showed "marked atherosclerosis", mortality from coronary disease was 0 55% In the investigation of Laurie and Woods,[1] 16% of the 300 aortas examined showed "severe atherosclerosis with ulceration, calcification, and gross scarring", the state of the coronary vessels was not recorded, not one subject was mentioned as dying from coronary occlusion, not even in the larger series mentioned of 2000 consecutive necropsies Strangely, this finding evoked no comment

The main purpose of this letter is to stress this disparity in the Bantu between the occasionally severe atherosclerosis of aorta, although to a lesser extent of coronary vessels, and the low mortality from coronary occlusion

Even in Dr Davies' extensive postmortem studies in Uganda, where mortality from occlusion is virtually nonexistent, he stated "At Mulago a very high proportion of Africans coming to autopsy over the age of 50 show marked atheromatous lesions[6]" If thickening, ulceration, calcification, &c, arise largely from a succession of thrombotic episodes, it is not easy to understand why progression of these episodes leading to occlusion and death does not occur more frequently in these people Presumably, the "severe degree of coronary sclerosis" held by Lober[8] to be necessary, speaking generally, for symptoms and death, is not attained The usual argument trotted out over the Bantu not living long enough to die from coronary thrombosis is untenable, in Johannesburg there are 60,000 Bantu over 45 years, and 9000 over 65 years Using Professor Yudkin's phraseology,[12] *predisposing causes* in at least a proportion of the local Bantu are certainly present (atheroma, hypertension, stress, and smoking), against these range the pattern of their diet, infrequent obesity (except in women of 20 to 40), greater physical activity, and liver disease[7,13] (with combined ramifications in low serum-lipid components, high plasma-fibrinolysin activity,[13] &c), the *precipitating causes* obviously are virtually absent

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1 Laurie, W, Woods, J D *Lancet*, 1958, i, 231
2 *Epidem vit Stat Rep*, 1956, 9, 537
3 *ibid* 1957, 10, 219
4 Annual Report, Baragwanath Hospital, Johannesburg, 1951–55
5 Annual Report, Johannesburg Public Health Department, 1956
6 Davies, J P N *E Afr med J* 1948, 25, 454
7 Walker, A R P *Conference on Hormones and Atherosclerosis*, Brighton, Utah, U S A, March, 1958 To be published
8 Lober, P H *Arch Path* 1953, 55, 357
9 *Brit med J* 1955, ii, 1016
10 Becker, B J P *S Afr J med Sci* 1946, 11, 107
11 Higginson, J, Pepler, P J *J clin Invest* 1955, 33, 1336
12 Yudkin, J *Lancet*, 1957, ii, 155
13 Gillman, T, Naidoo, S S, Hathorn, M *ibid* p 696

Professor McMichael considers that "strong emotional devotion to corn-oil diets or anticoagulant pills will do no good to medicine" Prof Ancel Keys,[14] possibly more colourfully, has derisively inveighed against those who entertain the view that the coronary-heart problem may be solved without retreating from present high-fat diets merely "by taking a daily swig of linoleic acid and a few vitamin pills" We concur with these views Mere attainment and maintenance of a "favourable" blood-lipid picture per se need not reduce the chance of dying from coronary-artery disease, we believe that for that "favourable" blood-lipid picture to be effective, directly or indirectly, it may well have to lie within a particular dietary and metabolic context Although most writers regard it as premature to recommend significant changes in diet to ward off death from coronary occlusion, our belief is that the only certain known way to do this is by adoption of the pattern of diet (with all its concomitant metabolic ramifications) consumed by the Bantu and similar populations For this viewpoint there is much evidence, published and unpublished, which one of us (A R P W) hopes to present in the near future It would be naïve, however, not to recognise that the likelihood of any marked change occurring voluntarily in the diets of Western populations, no matter how frightening is the increasing mortality from coronary disease, is so remote as scarcely to merit serious discussion

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ALEXANDER R P WALKER.

Baragwanath Hospital and South
African Institute for Medical
Research, Johannesburg
I W SIMSON

NEW METHOD OF PHENOBARBITONE ADMINISTRATION

SIR,—I thank Dr O'Connor (May 3) for his reply

(1) I have accepted his facts and have said, giving reasons, that from them no conclusion can be drawn about the value of 'Spansule' phenobarbitone If its value was so great, why had other anti-convulsants to be simultaneously given, sometimes in increasing doses?

(2) The description of the rigid routine for administration of drugs, and the statement that the same nurses had attended the patients for a number of years, are new, though not very precise, data They do not amount to the required guarantee, especially with patients who were spiteful, cunning, paranoid, hostile, and suspicious

(3) There is a confusion here between improvement of personality, in which we all hope that psychotherapy has a great future, and relief from epilepsy, in which we all agree that it has not

(4) Added interest and stimulation on the one hand, and increased medication on the other, are not mutually exclusive alternatives I said, and meant, "may have helped"

(5) "Either wholly or in part"—there's the rub

(6) If 18 patients with, say, a hitherto invariably fatal disease were given a certain drug and all recovered, that number would be superfluously great for proof, but where everything is a matter of degree and careful assessment, 20 is nearly always the bare minimum I did not mention inert substances, the comparison should be with the same dosage of ordinary phenobarbitone, as suggested by Dr Pearson (April 19)

(7) "Striking" does not mean convincing There is no conflict here Kurtzke and Berlin's data were impressive except for two flaws the control series, having been earlier than the treated series, was studied retrospectively, and in the treated series both patients and doctors knew who was receiving a new treatment The parallel is close, and instructive to anyone who sees the same general difficulties in all therapeutic trials

Dr Levitt (May 10) seems to say that the paper is open to criticism but we ought not to criticise it I agree with him that the method may be of great value, would he agree with me that equally it may not? That is what I mean when I say that no conclusion can be drawn from the present data If I had thought that they should be ignored I should have ignored them instead of writing a letter about them

Perhaps we may now all agree to await the results of a controlled clinical trial

London, W 1
JOHN PENMAN

THE Y CHROMOSOME IN MAN

SIR,—Both the true hermaphrodite and the man with the uterus referred to in my letter of May 3 have elastic tissue surrounding the hyalinised seminiferous tubules of their testes This distinguishes them from Dr Ferguson-Smith's latest description of chromatin-positive microrchidism (May 3, p 928) It also alters the premises on which I based my argument on the function of the Y chromosome

Department of Anatomy,
The Medical School,
King's College,
Newcastle upon Tyne.
JOHN GRAY

"THESE DYING DISEASES"

SIR,—The paper by Mr Ambrose King (March 29) concerning present-day problems of venereology was timely, especially in regard to gonorrhœa, in which there is the alarming situation of an increasing number of cases and an apparent lessening sensitivity of the gonococcus to penicillin

The number of new male cases of gonorrhœa seen in the clinics of England and Wales has increased by approximately 28% during the last two years, and the current figure for both sexes is virtually the same as it was as far back as 1949 At the same time doses of repository penicillins, which were once 95% effective, today produce far less satisfactory results Indeed, in recent series treated with single doses of 1 2 mega units of procaine penicillin with aluminium monostearate or of benzathine penicillin, failure-rates in the range of 18%–30% have been encountered

While similar experiences have not so far been widely reported in the U S A, the situation is certainly not confined to Britain At the recent World Health Organisation seminar in Tokyo it was evident that the declining powers of penicillin in gonorrhœa had been widely noted in the Far East Indeed, in a "sex store" in Yokohama, where I asked the proprietor what he used for gonorrhœa (drug-store treatment being legal in Japan), I was informed that for some time he had employed the tetracycline antibiotics, because penicillin was no longer effective

It is not known for certain whether the gonococcus is developing alternative metabolic processes or whether, as seems more likely, the apparent lessened sensitivity is arising from repeated selection of the more insensitive strains Further research is required In any event it seems that higher doses of shorter-acting penicillin preparations are required to provide higher peaks of penicillinæmia than are obtained with repository penicillins which the gonococcus now seems capable of overcoming This would mean the sacrifice of the so-called "epidemiological tail" provided with repository penicillins which act during the time that the consorts are being traced and which reduce the possibilities of reinfection of the original patient, and at the same time help to reduce the reservoir of syphilis "All-purpose" penicillins, by providing a higher initial level, and also a prolongation, at present give better results and might provide the answer, but, on the other hand, the existence of the " tail " itself may foster further relative resistance of the gonococcus

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[14] Keys, A *ibid* 1956, i, 576

The treatment of gonorrhœa today presents a difficult problem and it was the consensus of opinion amongst participants at Tokyo that the deteriorating situation would tend to continue with increasing numbers of cases and further evidence of lessened sensitivity of the gonococcus to penicillin There is certainly no place for complacency

London, W 1 R R WILLCOX

AN EOSINOPHIL COUNTING CHAMBER

SIR,—Ever since the assessment of pituitary and adrenocortical function began to attract increasing attention, there has been much controversy about eosinophil counting New methods and techniques are proposed from time to time, but none seems to solve the problem It seemed to me that it would be better to concentrate on finding out the reasons for the shortcomings of the well-known acetone methods, which are far superior in their clarity, rather than use fluids whose viscosity and colour make it hard to identify the cells In spite of the meticulous care of analysts and statisticians, there is still something which confuses results when acetone diluents are used Fractions of the same blood sample treated by the Dunger, Rud, or other methods, give contradictory results under identical conditions, and simple experiments showed that even fractions of the same mixture, led simultaneously through pipettes to chambers of various capacity, gave results differing by from 30% to 50%, as the volume of the chambers was increased [1]

These findings suggested that the trouble lay in the way in which the cells sedimented in the chambers I found that during sedimentation the peripheral cells were driven towards the centre of the chamber, where cells accumulated, thus seriously affecting the accuracy of the count In all types of chambers, the periphery was depleted in this way when acetone was used On the other hand, this phenomenon was not noted in chambers filled with blood and other hæmatological fluids not containing acetone

It occurred to me that the cause of this migration (which is a phenomenon distinct from Poisson distribution) was the contact between air and acetone-containing fluid at the edges of the chamber, and I sought to overcome the difficulty by designing a chamber which would completely eliminate contact between drops and air during the counting

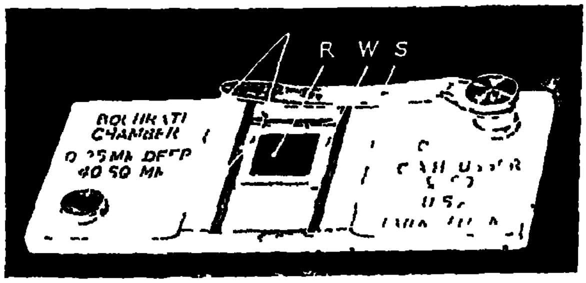

Fig 1—Photograph of counting chamber

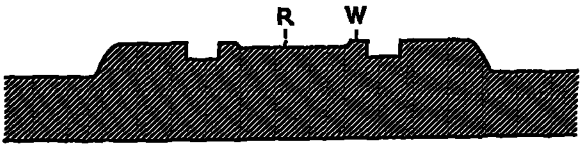

Fig 2—Longitudinal cross-section

In this chamber (figs 1 and 2) a wall (W) surrounds the ruled area (R) and prevents the drop of fluid in the chamber from coming in contact with air A support (S) holds the coverglass in contact with the drop Fig 3 shows how this chamber eliminates the migration which takes place in other types of chamber

A rectangular ruling (8×5 mm), in the Fuchs-Rosenthal pattern, gives large columns for easy reading It is unnecessary to load the chamber more than once for any particular count The ruling is divided into fourths by double median lines, thus permitting a count of half or quarter of the ruling in intense eosinophilia The big volume of the chamber (10 c mm) *means that the total count gives directly the number of* cells per c mm of blood, using a dilution of 1 in 10 The shallowness of the chamber (0 25 mm) overcomes the difficulty of sedimentation so common with deeper chambers The walls are inclined so that no foreign bodies can stay in it when the chamber is being cleaned Preparations can be left in the chamber almost indefinitely, and wet boxes are no longer needed The cells can be coloured in the chamber proper, without risk of desiccation or removal of cells

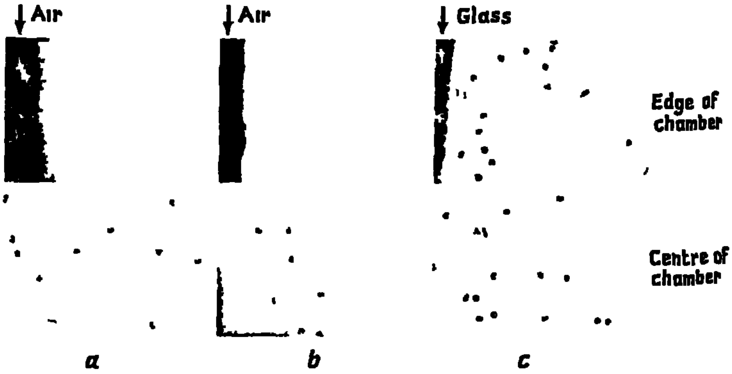

Fig 3—Photomicrographs illustrating migration in (a) Jessen chamber (0 4 mm depth) and (b) Fuchs-Rosenthal chamber (0 2 mm depth), and absence of migration in (c) Boghrati chamber (0 25 mm depth)

The distributors of the chamber are Evertex AB, 29, Stortorget, *Malmo, Sweden*

New York N BOGHRATI

RETROLENTAL FIBROPLASIA

SIR,—Your recent suggestion (April 26, p 893) to abandon the term " retrolental fibroplasia " and replace it by " oxygen-induced retinopathy of prematurity " may give rise to certain difficulties

For the past four " oxygen-conscious " years we have continued to examine the ocular fundi of all infants in the premature nursery of Babies Hospital at weekly intervals During this period there were 1060 admissions of infants whose birthweight was below 2000 g Five individuals developed retrolental fibroplasia, a substantially reduced incidence of this distressing condition as compared with four previous years Three of these infants had experienced only the briefest exposures (minutes) of supplementary oxygen and never in concentrations above 40% The ocular disease in these infants was in no way different from that observed previously in our nursery in many infants following prolonged exposure to high concentrations of oxygen

It is important to admit the possibility of the (rare) occurrence of retrolental fibroplasia as the result of exposure to only atmospheric concentration of oxygen (21%) An accurate history of " no supplemental oxygen " does not exclude the possibility of this disease The term " oxygen-induced retinopathy of prematurity " may be technically correct and

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1 Boghrati, N *Brux méd* 1954, 34, 1945, 1999

does not exclude these rare examples that occur after exposure to 21% oxygen. I am concerned, however, that the use of this term will result in the erroneous exclusion of these cases in future reckonings because of misinterpretation of the limits of this category Our best interests will not be served if retrolental fibroplasia is spuriously eradicated by a glossological manœuvre.

Babies Hospital,
New York.

WILLIAM A SILVERMAN

A FIFTH MALARIA PARASITE OF MAN?

SIR,—Kindly permit me to make the following observations with regard to your annotation [1] on this subject.

Sinton and Mulligan [2] made a successful transmission of *Plasmodium knowlesi* to a monkey with *Anopheles annularis* and not *A maculipennis* as you stated.

The following report [3] regarding *P knowlesi* as a human infection, published in 1952, is also of special interest since it is based on an attempt at sporozoite-induced transmission, while the other reports, so far as we know, are based on trophozoite-induced transmissions

> "Differences in susceptibility of man to sporozoite- and trophozoite-induced infections of *P knowlesi* are also known Ray (personal communication in 1951) caused three batches of five specimens of *A annularis* harbouring sporozoites of *P knowlesi* to bite three human volunteers * After biting the human volunteers, each mosquito was dissected and the residual sporozoites were inoculated into three monkeys all of which took the infection Blood films of the volunteers were examined periodically and not one of them developed the infection in the course of ten months of observation About the same period, two white mice were inoculated each with two mosquito equivalents of *P knowlesi* sporozoites, and no infection could be detected in them during two months when their blood smears were examined daily Man, as already stated, is susceptible to blood-induced infections of *P knowlesi* but not to sporozoites White mice on the other hand are not susceptible either to sporozoite- or blood-induced infections of *P knowlesi* "

There is a mistake in reference 12 the name of one of the joint authors is Nair and not Mair.

Malaria Institute of Delhi,
India.

S P RAMAKRISHNAN
Deputy Director

*** We are grateful to Dr Ramakrishnan for pointing out our two mistakes —ED L

DEATH OF A BOXER

SIR,—Having spent most of my active sporting life in the ring, I feel I should understand both the physiological stresses and the pathological lesions of the art of self-defence I was lucky in having a precisely developed postman's knockout punch to win six Irish university titles (1924–29), three British university titles (1927–30), and the heavyweight title of the R N V R. (1931)—all on knockouts None of my opponents ever suffered from any after-effects, and in all my close contact with boxing over thirty-five years I have never seen any permanent lesions caused by it. This great British game teaches a man to stand up and face both physical and moral stresses, which in my own eventful career has stood me well

I foster and admire the noble art, and in this town we have one of the finest boxing clubs in Kent.

Of course there are inherent dangers in all sport, as in life in general, but under proper medical supervision and the rules of the A.B.A and the B.B B C, character, the British bulldog breed, and fair play are fostered.

Tunbridge Wells

E F ST J LYBURN

TREATMENT OF ASTHMA AND HAYFEVER BY HYPNOSIS

SIR,—This correspondence seems to provide data for an observation in what is probably the realm of social psychology or even anthropology three out of five of your correspondents have either not read the original paper with any attention, or have failed to understand it. Dr Moynahan (May 17) might not admit this sample of professional men as statistically significant, but we feel that such a finding of 60% among even a single group is unlikely to be without cause. As one possible interpretation we would point out the emotional affect still apparently engendered by the word " hypnotism "—much as it was by " mesmerism ' in the days of Lavoisier, recalled in Dr Moynahan's letter—and the suspicion or even distortion, of the facts, which such affect can produce in an observer

Our object in carrying out the experiment was quite clearly stated in the opening paragraph noting, with references, the value of hypnosis as a means of symptom relief (not cure) in allergic conditions, we then told how we " tested a patient's skin reactions to known allergens during the relief of associated allergic symptoms by hypnosis "—and we recorded our results. While endorsing Dr Moynahan's views on the education of present-day medical students in statistics and probability theory, we do not, however, believe that all experimental results are necessarily dependent on statistical analysis—although we admit, incidentally, it often seems that almost any result can be obtained (or refuted) by statistics

In our paper, therefore, we made no " therapeutic claims based on a solitary case " (Dr Moynahan), " good evidence of the value of hypnosis " (Dr Franklin, May 17) was not presented, since this was taken as read, and we never denied in any way that " individual case-histories can readily be matched from patients treated by either psychological or allergic methods." (Dr Pepys, May 10) Dr Pepys, in fact, was so busy submitting our report to " critical analysis " that he wrote of the " repeated vigorous skin testing (10 pricks were made into each site compared with the one prick commonly used for diagnosis) " From this he then proceeded to draw a whole series of conclusions The method used, however, was not the " prick test " at all, but the less traumatic and less desensitising technique of " multiple pressure ", with which the other was carefully compared at the outset Describing our actual tests we wrote " Multiple pressure through the drop was then exerted ten times, without scratching, with a sterile hypodermic needle "

Dr Pepys also suggested that " the inhibition by hypnotic suggestion of a single test on the left leg performed immediately on waking from a deep hypnotic trance, could be attributed to the well-known modification of peripheral circulation by hypnosis " This, of course, is possible, but if Dr Pepys consults table I of our paper, he will be able to count no less than 16 positive urticarial reactions recorded as a result of skin testing immediately " on waking from a deep hypnotic trance " On the one occasion, however, when direct suggestion was made that all skin reactions should be inhibited, there was no reaction on the left leg after testing—and we took this to be significant.

The problem of possible local hyposensitisation raised by Dr Pepys and subsequently by Dr Blair Macaulay (May 17) is of more interest and presents one of the inherent difficulties in designing experiments in this field as does the possible development of an anaphylactoid response when working with other materials

In general it will be found that different parts of the body give different degrees of allergic response to the same allergen when tested at the same time, but that the same part of the

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1 *Lancet*, 1957, ii 932.
2. Sinton, J A., Mulligan, H. W *Rec. Malar Surv India*, 1933, 3, 351
3 Prakash Satya Krishnaswami, A. K., Ramakrishnan, S P *Indian J Malar* 1952, 6, 179

* " One of the volunteers had never experienced any malarial infection at any time while the other two had malaria prior to 1943, 8 years previously, and underwent a radical cure.'

body tends to give approximately the same degree of reaction when tested over a period of time Tests on different parts of the body to avoid the possibility of local hyposensitisation would therefore be unsuitable for comparison and the results of the experiment meaningless Comparable tests were therefore carried out on the left forearm—though not exactly on the same spot each time—and the " prick test, the modified prick test, the scratch test, and the intradermal test " were all rejected in favour of multiple pressure, in the hope of minimising local hyposensitisation As it turned out this approach was reasonably successful According to the notes the patient in this case was seen on July 22, 1957, when her personal " hayfever season " was over and her full skin sensitivity was returned to her by direct suggestion under hypnosis Tested after waking on the left forearm, the responses were recorded on ' Sellotape ' in the usual way and stuck in the notes, though the actual areas have not been calculated by lead tracing and weighing They appear, however, to be approximately equal to those recorded during the third week of treatment, when the figures were B2, 139 sq mm , B3, 33 sq mm , and B8, 25 sq mm We apologise for not including these facts in our report

In this and further experiments on which we have worked, or are now engaged, hypnosis as such is not under investigation as a therapeutic agent, as Dr Moynahan and others seem to have assumed It is either being used incidentally for treatment in routine psychiatric practice (as in the case recorded), or we are employing it as a tool with which to manipulate psychosomatic and other phenomena in suitable volunteer hypnotic subjects Under investigation in both these cases are the physiological and serological changes influenced by hypnosis, and these occur particularly in association with conditions generally described as " allergies " von Pirquet[1] coined this term " allergy " as descriptive of " an acquired alteration in the capacity of living tissues to react " with specific reference to " old tuberculin " in sensitised subjects We have also investigated the psychic element involved in this, " the original allergy " Pace Dr Pepys (of the Tuberculosis Research Unit), we will shortly be publishing a paper which records the inhibition of a positive Mantoux reaction by means of suggestion under deep hypnosis thereby producing an individual Mantoux-positive in the left arm, and Mantoux-negative in the right At a subsequent session, this state of affairs was reversed, and the subject became Mantoux-positive in the right arm and negative in the left

We wish to thank your correspondents for their interest in our work

West London Hospital,
London, W 6

A A **Mason**
Stephen Black

INTERMITTENT ALDOSTERONISM IN PERIODIC PARALYSIS

SIR,—We have read with much interest the article by Conn et al on periodic paralysis[2]

The principle of the salt-restricted diet, advocated in this study, has been applied to two patients with periodic paralysis We have not been able to confirm the hopeful results claimed by Conn et al

In one patient, who had severe paralytic attacks at least once a week, neither a diet containing 20 (or even 10) mEq of sodium daily, nor the combination with desalting procedures, prevented the recurrence of these spontaneous attacks

In his sister, who had a mild form of the disease, the administration of glucose and insulin, which provoked an attack on a normal salt intake, did not result in an attack when a salt restricted diet was given It seems as if the effect of the salt restricted diet depends on the severity of the disease

We have been able to confirm the retention of sodium (and of chloride) during the attacks This did not, however, precede clearly the retention of potassium and did not seem to be essential for the occurrence of an attack

Department of Endocrinology and
Metabolic Diseases,
University Hospital,
Leiden, Holland

J **de Graeff**
J S H **Brocker**

EXTRACORPOREAL CIRCULATION

SIR,—I was much interested by your leader of May 17 I feel sure that many of us feel guilty in not having supported Professor Ian Aird and his team at the Postgraduate Medical School more wholeheartedly It is good to see the Postgraduate machine coming into its own

In Birmingham, we use the Lillehei-DeWall system and find its application to human patients admirable and it has entered the hospital routine In the last paragraph of your leader you mention that the main charge should fall henceforth on the National Health Service, and I do hope this advice will be heeded The establishment of a working heart-lung bypass apparatus in this hospital has been possible only because of a generous grant from the Endowment Research Fund, supported by one from the University of Birmingham

During the last year a team, always the same in personnel, has been working regularly and continuously in the laboratory Four medical members of the team and two whole-time technicians have mastered the techniques, and the same team is now operating in the hospital theatres Such a transition is expensive and as soon as it is taken over by the hospital authorities a financial allocation will be necessary for the continuance of the work, which is now long beyond the experimental stage

Birmingham

A L **d'Abreu**

AMERICAN REACTIONS TO THE STAPHYLOCOCCUS

SIR,—Your enlightened editorial of May 17 contains the seeds of progress, in the phrase " nobody has power to act " The general establishment of the post of hospital infection officer is merely another sop to the sleeping Cerberus, unless " he has power to act " Action is what is needed

An account of a successful eight-year effort to keep a well known maternity hospital free of infection was recently refused publication, probably because it contained too much boring detail If this detail is too boring to *read*, how much more boring it must be to *effect* in actual practice, unless one judges rather by results than by the deadly day-to-day routine

New lamps for old is still the cry, but Aladdin knows his literature, and clings to his ancient source of enlightenment The matrons still hopefully polish the lamp of Florence Nightingale but the genie eludes them Anyway, we have it on very good authority that Florence Nightingale did not believe in bacteriology[1]—or faeries either, probably

What is really needed is the atmosphere described so effectively by a very great and gracious Lady recently in Liverpool[2] she said, " Visitors are conscious of a pulse like a hammer and a vigour which nothing can daunt "

St Margaret's Hospital,
Epping, Essex

Frank Marsh

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[1] von Pirquet, C F *Berl klin Wschr* 1907, 48, 644, 699, *J Amer med Ass* 1909 52, 675

[2] Conn J W , Louis L H , Fajans, S S , Streeten, D H P , Johnson, R D *Lancet*, 1957, i, 802

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[1] Cope, Z Florence Nightingale and the Doctors London, 1958

[2] See *Lancet*, May 17, 1958, p 1067

TOXÆMIA OF PREGNANCY

SIR,—Professor Theobald (May 10) asks me three questions First he says

> "Infants, non-pregnant women, and men die from renal cortical necrosis If toxæmia of pregnancy results from cortical ischæmia, why is eclampsia peculiar to the pregnant state?"

Briefly the answer to this is that in pregnant women (but not in infants, non-pregnant women, or men) cortical ischæmia is associated with retention of salt and water

Secondly, he asks why—if resistance to uterine stretch is the stimulus which provokes renal ischæmia—bilateral cortical necrosis practically never occurs in primigravidæ but is commonest in multigravidæ with accidental hæmorrhage The reason is that the extreme bursting force resulting from a concealed accidental hæmorrhage causes the extreme degree of renal shut-down that is characteristic of cortical necrosis

Thirdly, he asks how it is that patients with true eclampsia may secrete urine freely For this there may be several reasons

(1) Preceding attempts at treatment (e g, intravenous glucose) may have provoked an osmotic diuresis

(2) Drugs such as veratrone and apresoline may have reduced the vascular resistance

(3) Restriction of salt may have caused diuresis, as it does in the presence of œdema.

Diuresis is not, as might appear, incompatible with renal cortical ischæmia On the other hand, of course, a mounting oliguria is usual with impending eclampsia

London, W 1 JOHN SOPHIAN

VISITING PARENTS IN HOSPITAL

SIR,—Florence Nightingale in her *Notes on Nursing* (1859) wrote

> "There is no better society than babies and sick people for one another Of course you must manage this so that neither shall suffer from it, which is perfectly possible If you think the 'air of the sick room' bad for the baby, why it is bad for the invalid too and therefore, you will of course correct it for both It freshens up a sick person's whole mind to see 'the baby' And a very young child, if unspoiled, will generally adapt itself wonderfully to the ways of a sick person, if the time they spend together is not too long"

Professor Illingworth's plea (May 10) is timely The struggle to achieve daily visiting to children in hospital was hard but the results justified the endeavour

One of the next steps in the "humanisation" of our hospitals is the provision for ill parents to have their children visit them The same arguments used against daily visiting, namely the spread of infection and the subsequent emotional upset to the child, prove in practice to be quite unfounded

London, W 1 DAVID MORRIS

SIR,—I would support Professor Illingworth's plea for allowing children to visit their ill parents in adult wards

For the past two years we have allowed the children to visit all wards, other than obstetric or tuberculous, for half an hour on Saturday afternoons The ward sisters agree that, on balance, it is a good thing and much appreciated by their patients

There are difficulties It is not easy to limit the number of visitors at any bedside to two All the children have to come visiting, since it is often not possible to arrange for the care of any left at home

Very occasionally a child has been upset by seeing some hospital activity—e g a blood-transfusion in operation Again, a noisy baby can be disturbing to an ill patient Nevertheless, a good ward sister can deal with these minor troubles, and we should not wish to deprive the adult patients of these weekly family gatherings

Whittington Hospital,
St. Mary's Wing,
London, N 19 CECIL D COYLE

BONE-MARROW TRANSPLANTS

SIR,—The recent fundamental work on immunological tolerance and bone-marrow transplantation in animals was expected to lead to an outpouring of reports on its clinical application Only one major clinical study, however, has been published to our knowledge—that of Thomas et al [1] The reason for this reticence is probably the lack of convincing evidence of clinical success or failure

The recent preliminary communication of Dr Humble and Dr Newton (Jan 18), who have used the intra-aortic route of injection, has not contributed essentially to the clarification of this problem It is unlikely that the intra-arterial injection of a marrow suspension would be more successful than the intravenous route, which has been found to be effective in mice and to a limited extent in man [1] The avoidance of removal of cells by the lung and the closeness of the bone-marrow area to be repopulated by the graft do not appear to be factors of sufficient importance to warrant the risk of intra-arterial catheterisation In the past, successful direct injection of a bone-marrow suspension into a marrow cavity has never been reported Nevertheless, such preliminary reports as the one by Dr Humble and Dr Newton are apt to stimulate clinical interest in a procedure which will undoubtedly become increasingly important

Our experience with a patient in whom bone-marrow transplantation was attempted as a desperate measure may be of interest

A 36-year-old man with Hodgkin's disease of two years' duration had previously been treated with X-irradiation to the mediastinum and nitrogen mustard After ten months' remission, enlarged nodes developed in both axillæ and supraclavicular fossæ, associated with malaise, weight loss, and slight fever He was treated with a total dose of 15 mg of tretamine (T E M) over ten days, and two weeks after the last dose was found to have severe purpura caused by aplasia of the bone-marrow (Hb 7 g per 100 ml, white cells 500 per c mm, platelets 11,000 per c mm, bleeding-time>one hour) Bone-marrow aspiration from three sites revealed empty spicules with only histiocytic elements Three pints of fresh blood was transfused and prednisone was started at a dose of 100 mg daily, which was later gradually reduced He improved symptomatically, but a week later only the hæmoglobin value had risen (to 10 g per 100 ml), and there had been no change in the character of the bone-marrow, the agranulocytosis, and the thrombocytopenia

It was decided to attempt a bone-marrow transplant For the purpose of follow-up, the genotypical blood-group combination of the patient had to be determined, but because of the preceding transfusions this had to be done by examination of the parents, who fortunately were available The patient's genotype was O, M, CDe/cDe Bone-marrow samples were obtained under operating-room conditions from four suitable volunteers, the fat was removed and the bone particles filtered out with a Swinny filter syringe The pooled sample was suspended in Tullis solution and injected intravenously About 3×10^9 nucleated cells were injected Four donors were

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[1] Thomas E D, Lochte H L, Jr, Wan Ching Lu, Ferrebee, J W. *New Engl J Med* 1957, 257, 491

N-positive and two donors E-positive (N and E erythrocytes, therefore, were suitable for survival studies in the recipient) Treatment with prednisone (40 mg daily) was continued Three days after the transplant, white cells were 4500 per c mm , with 75% polymorphs, and six days later, the platelet-count was 109,000 per c mm The reticulocytes started to increase (4 2%, red cells $4\ 5 \times 10^6$ per c mm)

Periodic bone-marrow examination revealed evidence of gradual recovery At present, seven months after the transplant and three months after the prednisone was stopped, hæmopoiesis appears to be normal, the nodes are no longer palpable, and the Hodgkin's disease appears to be in remission Weekly examination of the blood-group pattern, by the technique of differential agglutination,[2] with the N and E erythrocytes used as "markers", revealed a concentration of 50–56% N cells and 30–40% E cells, maintained for ninety days after the transplant and ninety-eight days after the transfusion Thereafter, the concentration declined, and a hundred and forty days later such cells could no longer be demonstrated

Unfortunately, because of the previous blood-transfusions, this cannot be considered absolute proof of a successful transplant Nevertheless, the possibility cannot be discarded that the graft was temporarily accepted and later rejected after the patient's bone-marrow started to recover, perhaps under the influence of prednisone Whatever the mechanism, the rapidity of recovery of this patient from tretamine-induced aplastic anæmia makes it likely that the injection of bone-marrow cells from four donors contributed to it

Veterans Administration,
Westside Hospital,
Chicago, Illinois

PAUL HELLER
VINCENT YAKULIS

CATARACT A BIOCHEMICAL PROBLEM

SIR,—It was rightly pointed out in your annotation, Prospects in the Prevention of Blindness (March 15, p 577), that cataract is not a "senile" affection and that its nature is still unknown However, it was quite out of keeping with the theme being developed to end by placing in opposition the "one major surgical problem"—cataract—and all the other causes of blindness, classed as medical

One of the greatest hopes for the prevention of blindness lies in the elucidating of the biochemical changes which the lens undergoes during ageing and cataract formation, and it is to be hoped that before very long this important and widely prevalent condition will be removed altogether from the sphere of the surgeon

East African Institute for Medical Research,
Mwanza, Tanganyika

D S MCLAREN

PAROXYSMAL NOCTURNAL HÆMOGLOBINURIA

SIR,—Dr Stratton and his colleagues (April 19) describe three cases of paroxysmal nocturnal hæmoglobinuria (P N H) in which severe hæmoglobinuria was stopped by infusion of clinical dextran

Some years ago, Crosby[3] stated that anticoagulants (especially heparin injections) lower the rate of hæmolysis "in vivo" But he repeatedly observed severe hæmolysis on cessation of heparin activity (referred to by him as "biphasic action") Thus he and many other authors warned against the use of heparin in P N H cases

During the last four years we have had the opportunity to treat 3 cases of P N H with heparin It was administered as an infusion, diluted in physiological saline in doses of 30,000–50,000 units per day Hæmolysis was immediately stopped It was even possible to carry out transfusions of whole blood during these infusions Furthermore, cessation of heparin activity was not followed by hæmolysis

Heparin infusion therapy was first published by us in 1955[4] Further details of the above treatment will be published in the German medical weekly *Klinische Wochenschrift*

Medizinische Universitäts-Klinik,
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H G LASCH
A LINKE
H H SESSNER
A VOLKER

TETANUS

SIR,—As your leader of May 10 suggests, the value of relaxants in the treatment of severe tetanus is still not accepted by all who treat this disease, but I am convinced that the number of reports of such patients recovering with relaxants will continue to grow I shall be publishing in due course details of two further cases recently treated successfully with succinyl choline and intermittent positive-pressure respiration (I P P R) These two patients had incubation periods of 8 and (apparently) 3 days, and periods of onset to major convulsions of 36 and 48 hours respectively

In the severe cases necessitating tracheotomy and relaxant drugs, respiratory paralysis must be produced and artificial respiration given with I P P R There is no advantage and considerable danger in trying to maintain a patient with sufficient relaxants to control the worst convulsions and not enough to depress respiration The care of this type of case throws a heavy burden on general hospital wards and I would make a plea for all such cases to be nursed in respiratory units when there is such a unit near at hand In a respiratory unit single cubicles are readily available and the management of I P P R is part of the normal routine

St Ann's General Hospital,
London, N 15

G DONALD W MCKENDRICK

IDENTITY DISCS FOR MEDICAL INFORMATION

SIR,—Although Dr Scott's generalisation (May 17, p 1069) that "considerable sections" of the civil population are actively immune to tetanus may sound, perhaps, overoptimistic, the fact remains that a not negligible number of immunised persons may be found amongst injured patients receiving attention in casualty departments As he so rightly states, there is much to be gained by ensuring that these people are given a booster dose of toxoid rather than an injection of A T S (Indeed, when there is incontrovertible proof of adequate immunisation in the recent past, even the booster may safely be omitted)

Unfortunately many of them (e g , young children, brought in from street accidents, unaccompanied by adult relatives) either cannot say anything about previous immunisation or give information which the casualty officer regards as of doubtful reliability In either case he tends to play for safety by administering A T S

The difficulty lies in ensuring that dependable evidence of previous immunisation shall always be available in times of emergency Record cards given to immunised persons, though important, do not appear to solve the problem, all too often the card is not at hand when most needed In a well-dragooned autocracy such information could doubtless be conveniently recorded by tattoo marks on the individuals concerned, but I imagine that few people in this country would take kindly to such a suggestion

One possible solution would be a return to the old wartime identity disc, worn on a bracelet or necklace A simple, but universally understood code could be devised whereby a great deal of information about a person's medical history could be packed into very small compass on the reverse side of an identity disc Items, other than the dates of toxoid injections, which might well be incorporated in the code are the individual's blood-group and warnings about such diseases as diabetes, epilepsy, hæmophilia, and allergy from which he might be known to suffer

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[2] Dacie, J V , Mollison, P L *Lancet*, 1943, i, 550
[3] Crosby, W H *Blood*, 1953, 8, 769

[4] Lasch, H G , Linke, A , Sessner, H H *Acta hæmat* (Basel), 1955, 13, 366

To be effective the scheme would need to be organised on, at least, a national basis But better still would be an internationally agreed code-scheme With the increasing prevalence of international travel, the World Health Organisation might investigate the possibilities of some such scheme

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T F ELIAS-JONES

SERUM-TRANSAMINASE ACTIVITY

SIR,—In a description[1] of a method for the estimation of serum-glutamic-oxalacetic-transaminase (GO-T) and glutamic-pyruvic-transaminase (GP-T), a provisional normal range was given for the units defined therein The serum-transaminase activity of 75 "normal" adults of both sexes has now been estimated by this method, and the statistical analysis of these results is shown in table I

TABLE I—SERUM-TRANSAMINASE ACTIVITY (UNITS)

—	—	Range	Arithmetic mean	Standard deviation	Statistical normal range (m±20)
GO-T	Men	35–107	70·43	±18·32	34–107
	Women	28–113	67·04	±16·54	34–98
	Total	28–113	68·73	±17·47	34–104
GP-T	Men	27–105	53·95	±20·25	13–95
	Women	17–92	47·95	±17·61	12–83
	Total	17–105	50·67	±19·21	12–89
$\frac{\text{GP-T}}{\text{GO-T}}$	Men	0·32–1·22	0·77	±0·19	0·39–1·15
	Women	0·24–1·15	0·72	± 0·24	0·24–1·20
	Total	0·24–1·22	0·75	± 0·22	0·31–1·19

No variation with age was noted The distribution curve, as found in other enzyme assays,[2] was slightly skewed to the right giving a "lognormal" type of curve[3] With such an assymmetric distribution it is impossible to define a normal range in terms of mean and standard deviation, and table II gives lower and upper 1% levels and lower and upper 10% levels[2 4] 80% of the distribution is enclosed by the latter figures and 98% of the distribution by the former, results falling outside the 1% levels may be regarded as abnormal

TABLE II—RANGE OF NORMAL SERUM-TRANSAMINASE ACTIVITY (UNITS)

—	Lower 1%	Lower 10%	Upper 10%	Upper 1%
GO-T	35	42	95	107
GP-T	22	28	78	92
$\frac{\text{GP-T}}{\text{GO-T}}$	0·28	0·42	1·00	1·12

Using the unit proposed[1] (namely, that which will transform 1μ mole of α-aminoacid to 1μ mole of α-ketoacid in one hour at 37 C under the conditions described), and expressing activity per 100 ml of serum as in tables I and II, we have assayed both transaminases in various pathological conditions and determined their ratio $\frac{(\text{GP-T})}{(\text{GO-T})}$ The ratio has been found useful, being within normal limits in cases of uncomplicated myocardial infarction and usually elevated in hepatic dysfunction The value of the determination in pulmonary tuberculosis, where levels are raised, is being studied, and its use is being investigated in the differential diagnosis of rheumatoid arthritis and rheumatic fever, where low and raised levels respectively have been found

Further details of these investigations will be published later

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Darlington, Co Durham
R ANTEBI

Group Pathology Department,
Barrow-in-Furness, Lancs
J KING

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[1] King, J *J med Lab Tech* 1958, 15, 17
[2] Wootton, I D P, King, E J, Maclean Smith, J *Brit med Bull* 1951, 7, 307
[3] Gaddum, J H *Nature, Lond*, 1945, 156, 463
[4] Wootton, I D P, King, E J *Lancet*, 1953, i, 470

UNILATERAL NEPHRECTOMY PREOPERATIVE TREATMENT OF HYPERTENSION

SIR,—Removal of a phæochromocytoma and unilateral nephrectomy are now standard operations for the relief of severe hypertension in appropriate cases The patient's life may, however, be jeopardised after otherwise successful surgery by the damaging effect on the kidneys, or remaining kidney, of the postoperative drop of blood-pressure This results in oliguria and may proceed to irreversible uræmia It should be stressed that the postoperative blood-pressure level at which this complication may occur is higher in a severely hypertensive than in a previously normotensive patient

It would, therefore, seem rational in these cases with sustained preoperative hypertension to precede operation by 3–4 weeks of medical treatment with ganglion-blocking agents, resulting in a gradual drop of blood-pressure During this period the necessary vascular adaptations may slowly take place in the kidneys and brain, with a much smaller risk of infarcting these organs This is never far removed when the blood-pressure is suddenly lowered drastically from any cause in elderly or severely hypertensive subjects

Sheffield Royal Infirmary
H J GOLDSMITH

FRACTURES OF THE PARIETAL BONE IN CHILDREN

SIR,—Mr Maurice Ellis[1] is incorrect in thinking that superficial collections of cerebrospinal fluid associated with linear fractures of the parietal region have not previously been reported The condition is clearly described, and indeed illustrated, in the first edition of Rowbotham's *Acute Injuries of the Head* Mr Rowbotham calls them traumatic meningoceles—a clear and descriptive term—and stresses their common occurrence in children owing to the relatively adherent dura in young people

I have encountered a number of cases, but the outcome has not always been as happy as in those described by Mr Ellis

In 2 the swelling has persisted and the underlying bone has been gradually absorbed so that a linear crack in the skull vault has become converted, over a period of six months or so, into an irregular oval defect in the skull Rowbotham also describes and illustrates this event, referring to it as malacia of the underlying bone and noting that at a later stage brain may also herniate through the skull defect It is because of this possibility that I believe that early dural repair is advisable A small bone flap is turned down over the affected area and the dural defect is repaired either by simple suture or fascial graft The torn dura is usually found firmly adherent to the bone and trapped in the fracture line

In a further instance a similar skull defect appeared at the site of a linear fracture although swelling beneath the scalp had subsided within a few days of injury

I feel, therefore, that dural repair is indicated in all these cases or, in default of such repair, careful radiological follow-up for at least a year

Department of Neurosurgery,
University of Birmingham
BRODIE HUGHES

SIR,—Mr Ellis describes a condition which is well known to neurosurgeons and those whose business it is to care for patients suffering from injury to the head It is commonly termed traumatic meningocele [1]

While it is usually found in children, it is also seen in adults There is no reason why it should be confined to the parietal region, and it does in fact occur in other positions over the skull I have also seen it occur over a fractured sacrum

Swansea
NORMAN WHALLEY

PARADOXICAL ELECTROCARDIOGRAM IN CORONARY EXERCISE TEST

SIR,—Dr Geoffrey Bourne's report [2] on the change of an ischæmic T wave to a normal pattern after exercise prompts me to report two experiences

Several years ago I was shown a series of electrocardiograms of a patient with raised S–T segments, typical of recent infarction, the tracing became normal after an inhalation of 90% nitrogen Perhaps I should add that I understand that the patient suffered no ill effects from this myocardial assault

My own experience concerns a 40-year-old lady referred to me by Dr James Power A rather routine cardiogram done in January, 1957, revealed flattened or inverted T waves in all leads, there was no clinical evidence of myxœdema, Addison's disease, coronary disease, or old pericarditis, and the patient was thought to be suffering from mild neurasthenia A further tracing done in August showed a like record, and an exercise-tolerance test demonstrated a normal electrocardiogram with upright T waves in all leads (All records were taken in a semi-recumbent position) I am at a loss to account for the cardiographic changes in my patient

Portiuncula Hospital,
Ballinasloe, Co Galway
MORGAN MCELLIGOTT

LEVEL AND STABILITY OF BLOOD-GLUTATHIONE AFTER SPLENECTOMY

SIR,—The presence of Heinz bodies in erythrocytes of about 55% of patients after splenectomy was reported in 1955 by Selwyn,[3] who also put forward evidence that phenacetin could be responsible for their appearance in some cases Recent investigations of favism and hæmolytic anæmias induced by several drugs (primaquine, sulphonamides, *p*-aminosalicylic acid, naphthalene) proved that these conditions, in which Heinz bodies also appear, arise in people with an intrinsic hereditary abnormality of erythrocytes

This abnormality is manifested by defective activity of glucose-6-phosphate dehydrogenase, and low unstable blood-glutathione (G S H), and defective incorporation of glycine into the G S H [4–9]

Heinz bodies have also been reported in hæmolytic anæmia of the newborn after administration of vitamin-K analogues [10] Zinkham and Childs [7] found a transient non-hereditary blood-glutathione instability in all the newborns so far studied [7] The latter is not connected with deficient activity of glucose-6-phosphate dehydrogenase, and may be corrected in vitro by addition of glucose or inosin to the blood [9]

In view of these recent developments, we thought it interesting to investigate whether the appearance of Heinz bodies after splenectomy was also connected with some glutathione abnormality

Another reason for interest in the blood-glutathione after splenectomy was the possibility that it might be influenced by a change in the erythrocyte population following the removal of the spleen (e g , increased number of target cells and total erythrocyte-count in thalassæmia after splenectomy [11])

We examined the G S H level and its stability in 16 patients, six months to four years after splenectomy, by the method of Beutler [4] The patients were Ashkenasian Jews originating from Eastern or Central Europe (9 cases), and Sephardic Jews from Iraq (4), Persia (1), and Yemen (2)

In 14 cases the glutathione was stable and its concentration within normal limits The mean G S H content was 68±12 4 mg per 100 ml erythrocytes (in 300 control cases mean G S H was 70±13 4 mg per ml 100) In the erythrocytes of 2 of these patients (women of East European origin) occasional Heinz bodies were found

In 2 patients (men of Iraqi and Persian origin) the G S H was low (27 mg and 40 mg per 100 ml erythrocytes) and unstable Its content fell to 6 and 3 mg per 100 ml as a result of incubation with acetyl phenylhydrazine Few Heinz bodies were found in the blood of 1 of these patients, while in the 2nd they were seen in about 1% of erythrocytes

In view of these findings we think that splenectomy does not cause blood-glutathione abnormality This conclusion is probably not contradicted by the finding of the G S H instability in the last 2 patients, because we have previously found this defect of erythrocytes in about 20% of Jews originating from Iraq or Persia [9]

ARYEH SZEINBERG
CHAIM SHEBA
AVINOAM ADAM

Government Hospital,
Tel-Hashomer, Israel

Medicine and the Law

A Conviction for Unlawful Killing

AT the Central Criminal Court on May 19,[12] Dr Louis Aimee Newton was found guilty of unlawfully using an instrument with intent to procure the miscarriage of a 35-year-old Australian nurse on Oct 11, 1957, and of unlawfully killing her by using an instrument Mr Justice Ashworth passed sentence of two years' imprisonment on the first conviction and three years on the second Dr Newton was found not guilty of manslaughter on the ground of professional negligence

According to prosecuting counsel, the nurse had consulted a psychiatrist, Dr Ellis Stungo, who had advised abortion because of her state of mind Dr Stungo communicated with Dr Newton, who carried out the operation for a fee of £75 After the operation he saw her to a taxi which took her back to her hotel The patient died in hospital two weeks later, and death was attributed to renal failure following abortion

Dr Stungo was charged with counselling and procuring Dr Newton to unlawfully use an instrument, but at the close of the evidence for the prosecution [13] defending counsel successfully pleaded that there was no case to answer and Dr Stungo was discharged

In evidence, Dr Newton said that he visited the patient at her hotel after the operation and he found her pulse and temperature normal, though she said she felt sick He thought she was making a slow recovery and in his judgment she was not sufficiently ill to get disturbed about He admitted that he was wrong in his diagnosis in the first place, but he denied that he was grossly or criminally negligent in his treatment.

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[1] Rowbotham, G F Acute Injuries of the Head, 2nd ed, p 51 Edinburgh, 1945
[2] *Lancet*, 1957, ii, 1320
[3] Selwyn, J G *Brit J Hæmat* 1955, 1, 173
[4] Beutler, E *J Lab clin Med* 1957, 49, 84
[5] Carson, P , Flanagan, C L , Ickes, C E , Alving, A S *Science*, 1956, 124, 484
[6] Sansone, G , Segni, G *Lancet*, 1957, ii, 295
[7] Zinkham, W H , Childs, B *Amer J Dis Child* 1957, 94, 420
[8] Szeinberg, A , Asher, Y , Sheba, C *Blood*, 1958 (in the press)
[9] Szeinberg, A , Sheba, C , Adam, A Data to be published
[10] Allison A C *Brit J Hæmat* 1957, 3, 1
[11] Fairley, N H *Trans R Soc trop Med Hyg* 1940, 34, 143
[12] *Times*, May 20, 1958
[13] *ibid* May 16

Dr R. A Brews said [14] he was familiar with the preparation used to procure the abortion, but he would not himself use it for this purpose The proper place for an operation of this kind was in hospital or in a properly equipped nursing-home. Prof J C McClure Browne said [15] that, having heard Dr Newton describe the operation, he thought his technique perfectly reasonable It was very difficult in the early stages, in this particular situation, to recognise anuria and he could understand somebody failing to recognise it.

Counsel for the prosecution suggested [15] that the evidence disclosed an illegal operation, and when it went wrong Dr Newton did everything he possibly could to avoid discovery In doing that he disregarded the skill he should have displayed in exercising his professional services

Summing up, Mr Justice Ashworth called this an unusual and important case. It was important from the Crown's viewpoint because if the jury took the view that this was a case of criminal abortion they might well agree that criminal abortion was more sinister and more difficult to detect when it took place in the high places of Harley Street than in the drab surroundings usually associated with the crime The emphasis was on the word "unlawful" the use of an instrument was unlawful unless it was used in good faith to preserve the life or health of the woman, and the Crown had to establish that it was not used in good faith.

Passing sentence, the Judge referred to the fact that Dr Newton's name was removed from the Medical Register from 1942 to 1947, after he had appeared before the General Medical Council for offences relating to false certification.

Obituary

CHARLES SYDNEY ATKIN

B.A, M B Cantab

Dr Atkin, who died at his home on May 9, came of a long line of Sheffield doctors His father, the late Dr Charles Atkin, F.R.C.S, his grandfather, and his great-grandfather all practised in Sheffield

Born in 1889, he was educated at Marlborough, Caius College, Cambridge, and St Bartholomew's Hospital, qualifying in 1913 After settling in Sheffield he was for some years a consulting physician at the Children's Hospital there, and during the war of 1914–18 served as captain in the R A M.C with the British Expeditionary Force

He was a fine athlete, a member of the Cambridge University hockey team, 1909–10 He played hockey for England against Wales, Scotland, and France in 1913, took part in the Olympic Games in 1920, and played against Ireland in 1921 He was also a good tennis player, representing the Hallamshire Tennis Club for several years Later he became a keen shot and fisherman.

W R S and E G M write

Dr Atkin's professional outlook reflected his family tradition of unstinted service, his university and hospital background, his knowledge of men in sport and war, and a long sympathetic experience in practice

He gave his patients, with all his medical skill, the kindliest understanding and his untiring devotion No patient ever found him unresponsive to a call for medical help or for moral support and encouragement—but his sympathies not seldom cost him more than the recipients knew

On medical boards—as member and later as chairman—his experience and insight, with his charitable tolerance, were a support to his contemporaries and an education to his juniors

Dr Atkin is survived by his widow, a daughter, and two sons, one of whom is a doctor, now the fifth generation of the family to practise in Sheffield

Public Health

Smallpox

A MAN and his wife have been admitted to New Ferry Smallpox Hospital in Cheshire There is known to have been contact between these patients and the original cases of smallpox in the district last month [1] The man is reported [2] to be seriously ill, but the wife's illness is described as mild. The man was admitted for a few hours to the isolation block of Clatterbridge Hospital before being transferred to New Ferry Hospital after the diagnosis had been confirmed. Contacts are being interviewed and offered vaccination

Eire in 1957

IN Eire last year [3] the birth-rate was 21 2 per 1000 population, which was 0 2 above the rate for 1956 The death-rate—11 9 per 1000 population—was also 0 2 above the rate in the preceding year The maternal-mortality rate was 1 31 per 1000 births registered, compared with 0 82 in 1956 The infant-mortality rate was 33 per 1000 births registered, and the neonatal mortality rate 22—compared with 36 and 23 respectively in 1956 The death-rate from tuberculosis (all forms) was 24 per 100,000

Parliament

QUESTION TIME

Temporary Posts Overseas

Mr JOHN TILNEY asked the Minister whether, in order to help ease the medical requirements of Commonwealth Territories and to expand the knowledge of tropical medicine and problems among members of the National Health Service, he would recommend the proleptic appointments of consultants so that they can do a tour of duty overseas before taking up such appointments —Mr WALKER-SMITH replied I am advised that the National Health Service Acts do not permit me to do so and I am not convinced that what is proposed would achieve the object in mind I am, however, considering various representations which have been made to me on the subject

Artificial Limbs and Appliances

Mr C SIMMONS asked the Minister whether he would indicate the steps now being taken to develop the work of the department of research and experiment to secure improvements in the design, performance and fitting of artificial limbs, and the extent of any cooperation which existed to secure precise information about new artificial limbs and appliances available in other countries —Mr RICHARD THOMPSON, parliamentary secretary to the Ministry, replied Since last year, the work of the research department at Roehampton has been under the regular supervision of a small executive committee of the Standing Advisory Committee on Artificial Limbs On the recommendation of these committees, a special plastics laboratory is about to be established The research staff keep in close touch with colleagues in other countries by correspondence, exchange of literature and samples, and by visits Two members of the staff are at present visiting research establishments in the United States

Poliomyelitis in the Vaccinated

Poliomyelitis developed in 1957 in 8 (5 paralytic), 5 (2 paralytic), and 6 (3 paralytic) children in the first, second, and third months respectively after two injections of poliomyelitis vaccine In one case, which occurred in the first month, the child had paralysis affecting the inoculated limb

Protective Helmets for Motor Cyclists

According to estimates made by the Road Research Laboratory, over 500,000 motor-cyclists (47%) now use protective helmets

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[14] *Ibid* May 15
[15] *Ibid* May 17

[1] See *Lancet* April 26, 1958, p 906, *ibid* May 3 1958, p 959
[2] *Liverpool Daily Post*, May 19
[3] Quarterly report on births, deaths, and marriages, December quarter, 1957, and yearly summary, 1957 Obtainable from Government Publications Sale Office, G.P O Arcade, Dublin Pp 78 6*d*

Notes and News

THE ROYAL SOCIETY

For almost a century, its conversaziones have been a notable feature of the annual programme of the Royal Society But it seems unlikely that, in all this time, the exhibits have ever presented a more striking series of contrasts than they did this year Among the demonstrations to be seen at Burlington House on May 15, one related to the tracking of satellites (including some recordings made that day of the newly launched Russian giant), and another to the study of dinosaurs' brains The results of natural selection on certain species of snails could be contemplated during a programme that also included a film on the problems of transonic flight And, though perhaps the most beautiful of all the exhibits was that showing the mode of formation of ice crystals at sub-zero temperatures, certainly the largest was a working model of Sceptre, the reactor in which temperatures of some four million degrees have been generated

The equipment for polar research, developed by workers of the National Institute for Medical Research, struck a topical note It included an improved type of sledging ration, a method of carrying liquid propane in lightweight containers for use as a fuel, and a fabric knitted out of very flexible insulated wire Underclothes made of this wire will, appropriately connected, function as resistance thermometers, and can then be used to measure skin-temperature But it is likely that the fabric will find its most important application in the construction of electrically heated clothing, for it can be worn next to the skin and will there produce a maximum heating effect for a minimum energy input

There were two other items of great medical interest Sir George Pickering and his colleagues at Oxford showed how they had been investigating the distribution of the pressor substance, renin, in the kidney The problem of separating the nephron into its glomerular and tubular elements had been overcome by invoking magnetic forces in an ingenious way The intact kidney was perfused with a suspension of magnetic iron oxide, the particles of which are filtered off by the glomeruli The kidney was then ground up in Locke's solution, and this suspension was passed in a tube through the field of a powerful electro-magnet The glomeruli were arrested by virtue of the oxide particles they contained, while the remainder of the mixture, containing the tubular fragments, flowed on The two fractions could then be assayed separately for their renin content So far the highest concentrations had been found in suspension of large glomerular fragments, with a segment of the renal tubule attached to them

New prospects in virology have been disclosed by the discovery of interferon, a compound developed in certain virus cultures which can inhibit the growth of other viruses treated with it Dr D C Burke and Dr Alick Isaacs demonstrated the formation of interferon in chick-membrane media inoculated with irradiated influenza virus, and its subsequent concentration and assay Though its mode of action is still in doubt (it may be an analogue of a protein substance, for which it substitutes in an essential metabolic cycle), it has already been shown capable of arresting the multiplication of several viruses in both in-vitro and in-vivo experiments

RESEARCH IN EAST AFRICA

Working in any country other than his own, the investigator may find himself in difficulty because of variations in local custom and methods An example mentioned in the report[1] of the East African Council for Medical Research concerns the water content of cereal foods if these are prepared by certain methods in vogue among African housewives, they may contain so much water as to make ordinary calculation of nutrient values invalid In other work done at the East African Medical Survey and Research Institute it has been shown that mild hookworm infestations do not affect absorption of food, but the effect of heavy infestations has yet to be investigated Surveys in certain districts showed that about 70% of school children were infected by hookworm, and about 90% by schistosomiasis

The Virus Research Institute has been working mainly on "arbor" (arthropod-borne) infections, and the Leprosy Research Centre (a third of whose cost is borne by the British Empire Leprosy Relief Association) has been conducting a therapeutic trial with diphenylthiourea The absorption of this drug is poorer than that of dapsone, but indications are that it is equally effective, and it has proved "remarkably free from toxic effects", in the 56 patients treated there have been no signs of upset of the liver or hæmopoietic system, and no mental disorder The trial is being extended from the Kenya Medical Department Leprosarium to other centres

The Trypanosomiasis Research Organisation reports the development of methods for keeping the parasites deep-frozen by means of solid carbon dioxide By this means trypanosomes of three species have been maintained in an infective state for seven months, and such properties as drug sensitivity have remained stable Using artificial media, trypanosomes have been cultured from blood in which they were scanty (though the method was not much more sensitive than microscopic examination), but not from cerebrospinal fluid Strains of the parasite have been found to vary much in oxygen uptake There is so far no evidence of a special stage of development of the parasite in the mammal, such as takes place with the malaria parasite, the changes in form in the host's blood are attributed to the action of the host's defence mechanisms Infection does not reduce the length of life of the tsetse fly

A GREAT AND INVENTIVE SURGEON

A selection[1] of 78 papers by Walter E Dandy has been published as a tribute to one of the greatest surgeons of all time The choice has been made in chronological order, beginning with accounts of Dandy's work on the blood- and nerve-supply of the pituitary body This work was carried out at the suggestion of Harvey Cushing, who was working in the "Dog House" (laboratory) at the same time as Dandy Dandy's work on infantile hydrocephalus and the circulation of the cerebrospinal fluid is included, it was his first great contribution to surgery and gave him international recognition Halsted, Dandy's chief, said of this feat, "Dandy will never do anything equal to this again Few men make more than one great contribution to medicine" According to Dandy himself it was something to do with publication of this work that led to a violent quarrel with Harvey Cushing The book is specially valuable for its reprint of the epoch-making article on ventriculography, published in July, 1918, while Dandy was still a resident (surgical registrar) The following year his work on air encephalography appeared

There has never been a more inventive surgeon than Dandy, and anyone on the point of claiming to have found something new should first inquire whether Dandy has written something on the subject Indeed, this book may serve to stay the hand of some enthusiastic writers It was Dandy who showed that total removal of acoustic tumours, provided the interior is first removed, gives better results than the intracapsular method of Cushing, and five years before the famous paper by Mixter and Barr, he described protruded lumbar disc as a cause of acute pressure on the cauda equina ("This lesion offers a pathological basis for cases of so-called sciatica, especially bilateral sciatica The lesion is cured by operative removal of the cartilage") Dandy was also the originator of sensory-root section of the trigeminal nerve through the posterior fossa, although his observations about the arrangement of the pain fibres are probably invalid He clearly defined glossopharyngeal neuralgia and cured the condition by intracranial division of the glossopharyngeal nerve But perhaps one of his most remarkable accomplishments was his successful clipping of the neck of an aneurysm of the internal carotid artery, sans angiography, sans electro-cautery, sans blood-bank, sans hypothermia, and *sans peur*

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[1] The East African Council for Medical Research Annual Report, 1956–57 Nairobi 1958 Pp 20 4*s*

[1] Selected Writings of Walter E Dandy Editors Charles E Troland, M.D., and Frank J Otenasek, M D, Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications *1957 Pp 789 112s 6d*

His article on spasmodic torticollis has not stood the test of time and should not have been included Dandy advocated intradural section of the sensory and motor roots of the first three cervical nerves bilaterally and section of both spinal accessory nerves in the neck, a procedure now abandoned by most neurosurgeons It would have been better to have included Dandy's work on tumours and cysts of the third ventricle. Some of the references are not fully quoted according to present-day conventions For the sake of the younger neurosurgeons and neurologists, a short biography might have been included

The authors and publishers are to be congratulated on the production of this valuable book

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University of Cambridge

On May 10 the following degrees were conferred

M.B , B Chir —W B Peeling, E. A. French.
M.B —R. A. Aiken (by proxy)

University of Sheffield

The following appointments have been made

Dr P F Harris and Dr Miles Taylor, lecturers in anatomy, Miss E L Jervis, lecturer in physiology, Dr J A Beardmore, assistant lecturer in genetics, Dr Geoffrey Haigh, demonstrator in anatomy, Dr Margaret Platts, honorary lecturer in medicine, Dr Derek Hobson, honorary lecturer in bacteriology, Dr J P P Bradshaw, clinical teacher in neurology, Dr W L. Tonge, clinical teacher in psychiatry

Royal Society

On Thursday, May 29, at 4.30 P.M at Burlington House, Piccadilly, London, W 1, Group-Captain W K. Stewart will give a lecture on the Institute of Aviation Medicine

British Society of Immunology

The next meeting of this society will be held at the National Institute for Medical Research, The Ridgeway, Mill Hill, London, N W 7, on June 13 and 14 The meeting opens on Friday, the 13th, at 1 45 P.M., with a symposium on gammaglobulin and antibodies, when Sir Charles Harington will be in the chair Further details may be had from Dr R. G White London Hospital, E.1

Discussion on Shock

The Faculty of Anæsthetists of the Royal College of Surgeons of England will hold a meeting on Saturday, June 14 at 10 A.M at the college, Lincoln's Inn Fields, London, W C.2, on shock and allied phenomena The speakers will be Sir Henry Dale, Prof W D M. Paton, Dr J B Wyman, Dr R. I S Bayliss, Mr Ruscoe Clarke, Dr L J Wolfson, and Dr R. I Bodman.

Chelsea Clinical Society

In the mountains of Albania Mr Julian Amery, M.P , was treated by a doctor aged 105, who had ridden for an hour to find him. At the annual dinner of the Chelsea Clinical Society on May 13, he spoke of his medical attendant's belief that we are moving into an era when everyone will live longer—about 200 years, the doctor thought. Mr Amery was hopefully interested in the reactions of Cabinet Ministers who found themselves in power for terms of 20 years rather than 5

Sir Walter Fergusson Hannay, the president, described the society as flourishing it has 283 members and has set its limit at 300 In the past year members had paid a visit to the crypt of St Bride's in Fleet Street, had heard talks on getting pleasure from painting, on nuclear warfare, and on the future of the independent school, and had held a clinicopathological conference Dr H S Pasmore, proposing The Guests, quoted Mr Aneurin Bevan on the folly of trying to make a good speech people expected a better one next time, and one's reputation was ruined The Earl of Halsbury replied to the toast

Inaugurating the new president, his predecessor said that, as secretary for 18 years, Dr Harry Coke was more than anyone responsible for the society's resuscitation after the war Dr Coke said that, on the contrary, the real resuscitator was Dr Desmond Macmanus, who had been president longer than anyone else He divulged that the salmon which had lately fed the entire company was caught by Sir Walter himself, in the Spey

Commonwealth Trans-antarctic Expedition

The Queen has approved the awards of the Polar Medal to the following doctors for good services as members of the expedition

Clasp to the Polar Medal —G W Marsh
Polar Medal —Rainer Goldsmith, A. F Rogers.

Women Candidates Only

Dr Marjory Keith, senior registrar at the Bruntsfield Hospital, Edinburgh, has been appointed to the post of consultant physician to the Bruntsfield and Elsie Inglis Hospitals which has been vacant since Dr Margaret Martin's retirement at the beginning of 1957 The South-Eastern Regional Hospital Board's proposal to join Dr Martin's post to vacancies at the Deaconess and Longmore Hospitals and advertise the combined post as open to a man or woman aroused controversy in Edinburgh which ended in ten women bringing a case before the Court of Sessions to restrain the board from appointing a man (see *Lancet*, 1957, ii, 1072) Lord Walker granted an order that no man should be appointed until the post had been advertised for women applicants only

Dr Keith's appointment, like Dr Martins, is at the Bruntsfield and Elsie Inglis Hospitals The vacancy at the Deaconess and Longmore Hospitals has been filled by the appointment as consultant physician of Dr R F Robertson senior registrar at the Edinburgh Royal Infirmary

New Atomic Safety Committee

Sir Douglas Veale, late registrar of the University of Oxford, is to preside over a committee set up by the United Kingdom Atomic Energy Authority to advise on training in radiological protection. This committee, whose members include Sir Ernest Rock Carling, Prof W V Mayneord, and Prof B W Windeyer, will advise the Authority on the training and provision of specialist health and safety staff, not only for the Authority's own purposes but also to meet the needs of the nation as a whole Sir Alexander Fleck's Health and Safety Committee, whose report was published last December, thought that the Authority should assume responsibility for building up the supply of the specialist health and safety staff required as the uses of atomic energy become more widespread Steps have been taken to build up the staff and recruitment is in progress

Hospital Progress

When he opened a new outpatient department at Nottingham City Hospital on May 16, Mr Derek Walker-Smith, the Minister of Health, said that as part of the Government programme of large centrally financed schemes, some 80 hospital buildings were in progress or had been selected for planning Among these 6 new hospitals had been begun, and 10 were at various stages of planning By the end of 1958–59 schemes which would cost about £30 million would be in progress Hospital boards also had schemes of their own choosing, from the money allocated to them, and there were some 45 further schemes of this sort in progress or proposed, costing more than £100,000 each, as well as many more smaller schemes But one of our chief aims, the Minister said, was to keep the patient, if possible, out of a hospital bed altogether, or, if he had to have a spell in one, to get him out of it as soon as this could safely be managed Mr Walker-Smith was glad that Nottingham, and soon Sheffield, were to have new outpatient clinics for these were important means of achieving his aim. Outpatient clinics helped in both, by undertaking diagnosis and treatment that would formerly have needed admission as an inpatient, and by providing follow-up care and supervision, which allowed a patient to go home after a short stay in hospital This shift of emphasis from inpatient to outpatient treatment not only led to a fuller and more economical use of expensive hospital service It was also of social benefit because, as Mr Walker-Smith pointed out, "people do not normally like to have to stay—especially for a long time—even in the best and most comfortable of hospitals and therefore the substitution of outpatient for inpatient treatment, and shorter stays in hospital, are likely to be of great social benefit both to the patient and his family"

Royal Air Force Appointments

Prof J B Kinmonth has been appointed honorary civil consultant in peripheral vascular surgery to the Royal Air Force Wing-Commander R S Peill has been appointed senior medical officer at the Royal Air Force College, Cranwell

Society for Relief of Widows and Orphans of Medical Men

The report of this society for 1957 shows that the membership now stands at 147 and that 25 widows and 2 orphans received grants During the year the society distributed £4000, including £2500 from the Brickwell fund At the end of the year the market value of the society's investments was £107,000 and during the year £2650 savings bonds 3% 1960/70 were bought The president is Sir Robert Young and the address is 11, Chandos Street, London, W 1

Social Security Agreement with Belgium

The convention on social security between the United Kingdom and Belgium, which was signed in May, 1957, has now been ratified and will come into force on June 1 It covers cash benefits for unemployment, sickness, maternity, old age, widowhood, orphanhood, industrial accidents and diseases, death, and family allowances Medical benefits under the Belgium health insurance scheme will be available to citizens of the United Kingdom who are employed in Belgium and to certain other people who are normally resident there

Gairdner Charitable Foundation

This Foundation, which was incorporated last year in Ontario, derives its funds from the gifts of Mr J A Gairdner, a Canadian industrialist and financier, and members of his family It has established the following international awards

Gairdner Foundation award of merit—A prize of $25,000 to be awarded not more than once in every four years to the individual or group of individuals who has made the most outstanding discovery or contribution in the fields of the arthritic, rheumatic, and cardiovascular diseases

Gairdner Foundation annual awards—A series of prizes of $5000 each to be awarded in any one year to not more than five individuals who have made outstanding discoveries or contributions in the same field

The first awards will be made during 1958, and further particulars may be had from the Foundation, 320, Bay Street, Toronto, 1, Ontario The medical advisory committee includes Prof R F Farquharson

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Dr E C Warner has been elected to the senate of the University of London as a representative of the faculty of medicine

Miss K A Raven has been appointed chief nursing officer at the Ministry of Health in succession to Dame Elizabeth Cockayne

Prof A D Macdonald, who is chairman of the Franco-British Pharmaceutical Commission, is leaving for France on May 22 to lecture at the Faculty of Pharmacy at Strasbourg and the Faculty of Science at Besançon

The Biochemical Society will hold a meeting in the Department of Biochemistry, Tennis Court Road, Cambridge, on Tuesday and Wednesday, June 24 and 25

Letters to the advice department of the Family Planning Association should once more be addressed to 64, Sloane Street, London, S W 1 The advice fee has been increased to 2s 6d

A working group in industrial health will form part of the 1958 summer school organised by the Central Council for Health Education at Bishop Otter College, Chichester, from Aug 19 to 29 Dr S F M Cressall will be tutor to this group

A travelling seminar, which has been arranged by the World Health Organisation, will visit France and England from May 19 to June 7 to study industrial medical services It will be led by Dr J J Gillon, senior medical inspector of factories of the Ministry of Labour in France, and Dr K Biden-Steele, deputy senior medical inspector of factories of the Ministry of Labour in England

The National Society of Non-Smokers held its first London clinic for the cure of tobacco-smoking on May 14, at Caxton Hall, Westminster, at 7 30 P M Dr Lennox Johnston, Dr Norman Macdonald, and Dr Wilfred Lester addressed the 60 smokers who attended The smokers were then split into groups for group psychotherapy Further clinics will be held on June 25 and July 9 at the same place and time

Diary of the Week

MAY 25 TO 31

Tuesday, 27th

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W 12
4 P M Dr J K Oates Reiter's Disease
INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Dr G C Wells *Use of Steroids in Dermatology*
INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
3 P M (Hammersmith Hospital, Ducane Road, W 12) *Prof J L Wright* (Otago) Anatomy of Prolapse
INSTITUTE OF CHILD HEALTH, The Hospital for Sick Children, Great Ormond Street, W C 1
5 P M *Dr G M Guest* (Cincinnati) *Studies of Insensible Weight Loss.*

Wednesday, 28th

ROYAL *SOCIETY* OF *MEDICINE*, 1, Wimpole *Street*, W 1
5 P M *Endocrinology* Dr Oswald Savage, Mr Geoffrey Slaney, Prof E G L Bywaters Complications of Long Term Steroid Therapy
POSTGRADUATE MEDICAL SCHOOL
2 P M Dr C H Andrewes Influenza—Asian and Otherwise
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P M Dr J R Bignall Course of Carcinoma of the Lung
INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
9 45 A M (Queen Charlotte's Hospital, Goldhawk Road, W 6) Professor Wright Toxæmia and Eclampsia in New Zealand
INSTITUTE OF DERMATOLOGY
5 30 P M Dr R T Brain Electrotherapeutic Techniques

Thursday, 29th

POSTGRADUATE MEDICAL SCHOOL
4 P M Dr Sheila Sherlock Hepatic Coma
INSTITUTE OF DERMATOLOGY
5 30 P M Dr Arthur Tickner Epidermal Proteins
HONYMAN GILLESPIE LECTURE
5 P M (Anatomy Theatre, University New Buildings, Teviot Place, Edinburgh) Prof Ian Aird Clinical and Operative Surgery of Parathyroid Tumours
UNIVERSITY OF ST ANDREWS
5 P M (Queen's College, Small's Wynd, Dundee) Prof Sir Stanley Davidson Megaloblastic Anæmias, with special reference to their Neurological Complications

Friday, 30th

ROYAL COLLEGE OF OBSTETRICIANS AND GYNÆCOLOGISTS, 58, Queen Anne Street, W 1
5 P M Dr J S Scott Pregnancy Toxæmia Associated with Hydrops Fœtalis, Hydatidiform Mole, and Hydramnios (William Blair Bell lecture)
ROYAL SOCIETY OF MEDICINE
5 P M Pædiatrics Dr A Doyne Bell The Force of Habit in Childhood. (Presidential address)
8 15 P M *Obstetrics and Gynæcology* Dr G R Osborn, Dr A E Claireaux, Dr Jean Smellie Neonatal Deaths
POSTGRADUATE SCHOOL OF MEDICINE
10 A M Mr E R Frizelle Thoughts and Impressions in Gastro-duodenal Surgery
ST MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W 2
5 P M Mr C W A Kimbell Carcinoma Corporis Uteri
GUY'S HOSPITAL MEDICAL SCHOOL, London Bridge, S.E 1
5 P M Dr H B Cott Protective Coloration in Animals (Fison lecture.)

Appointments

AUNGLE, P G, M B Edin, M R C P E, D P M consultant psychiatrist, Dundee Mental Hospitals
CUSACK, ANNE L J, M B Dubl, D P H assistant M O H, north-eastern area, Warwickshire

Birmingham School Health Service

CARVILL, P B, L R C P I M O
MARSHALL, BARBARA S M, M B Birm M O
VILLIERS, G I L, M B Dubl M O

London County Council

GRAEME, M L M B Cantab, D P H M O
MAHON, T J, M B N U I, D C H, D P H M O
ORTON, W T, M B Belf, D P H M O
WATTON, R W, M B Lond, D P H M O

Colonial Appointments

AUDEN E F, M B Edin M O, British Honduras
CARAPIET, A M, M B Calcutta M O, Somaliland
CHUNG HONG WING C C, M B N U I M O, *Mauritius*
DAS, J B, M B Madras, F R C S M O (grade B), Trinidad
MCGOWAN, ANGUS, M B Glasg M O, Hong Kong
MCLAREN, ROBERT, M B St And, D P H M O, Trinidad
MARCHANT, D E, M B Lucknow, D P H M O (grade C), *Trinidad*
TAYLOR, R J, M B Leeds M O, Tanganyika

The name of the Association of British Insecticide Manufacturers has been changed to the Association of British Manufacturers of Agricultural Chemicals

Semi-permanent exhibitions will be held at the Institute of Dermatology, Lisle Street, London, W C 2, during the summer term The first, from June 2 to 30, will be by Dr R W Riddell on skin reactions to fungus antigens

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TIME AND THE NERVOUS SYSTEM *

THE BRAIN AS A CLOCK

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> "We know how dangerous it is to over-estimate intuition Let us first ask a simple question What is a clock?"
>
> EINSTEIN and INFELD 1947

THOUGH present-day civilisation depends to a great extent on the administration of time (Government time), through the use of clocks, for its social and scientific progress, there is no *system* of knowledge about time, to compare with the advanced systems of biology, physics, and chemistry In neurology, which lies at the junctional point of philosophy and science, our interests have, until now, been limited to the spatial aspects of our subject We have therefore constructed the principles of clinical neurology, neuroanatomy, and neurophysiology in terms of space, thus

Clinical Neurology

Localisation of lesions
Representation of functions
Attribution of normal functions to parts, when symptoms follow damage therein
Reflexological tests concerned with "levels" in the nervous system

Neuroanatomy and Neuropathology

The spatial extensions of nervous tissues
Detection of disease processes by deduction from the state of tissues after removal and chemical processing

Neurophysiology

The operational study of isolated nervous structures according to theories derived from contemporary (electrical and chemical) technology.

The dramatic fragments of *temporal* neurology are treated as curiosities, or relegated to the neglected interstate between neurology and psychiatry For example, *amnesia* (from head injury, intoxication, epilepsy, encephalitis, or intravenous anæsthesia), the meaning of the alpha-rhythm of the electroencephalogram, and the "deja-vu" sensation of uncinate epilepsy, are all unrecognised as signposts in the exploration of the time sense.

There is now a worldwide awakening of interest in the problem of time and times Neurology is in the best position for the investigation of disorders of the time sense, and for the coordination of work in the fields of behavioural physiology and anatomy, navigation, electronics and computers, and "automation" generally

This contribution is a *summary* of thought on the human time sense, derived from clinical study To understand the main proposals of this work—that (1) animals contain immense numbers of clocks, from which the nervous system transmits and registers the time information, and that (2) the nervous system itself is a very complex clock-system—one must first consider the principles of chronometry

Chronometry

Definition of a Clock

The following definitional comments of clock forms are provided by Einstein and Infeld (1947)

"The primitive subjective feeling of time flow enables us to order our impressions, to judge that one event takes place earlier, another later But to show that the time interval between the two events is 10 seconds, a clock is needed By the use of a clock the time concept becomes objective Any repeated physical phenomenon may be used as a clock, provided it can be repeated as often as desired Taking the interval between the beginning and the end of such an event as one unit of time, arbitrary time intervals may be measured by repetition of this process All clocks, from the simple hour-glass to the most refined instruments, are based on this idea"

A definition of the strictest kind, expressed in the language of scientific logic, has been provided for me by Prof J H Woodger

"R is a clock if and only if R is an A-line, every member of the field of which has the same duration as any other member, and the beginning and end in time of every member of the field of which is visible, audible or palpable"

It is exceptionally important to note that no clock mechanism fulfils its purpose as a clock unless its activity is perceived by an observer, who understands the manner in which the clock possesses the attributes of a timekeeper

The clock of everyday use consists of a powered mechanism, driven by a coiled spring, or weight and pendulum (their power derived from the person who winds them) or electricity Two principles are used

1 The continuous motion derived from the power source is broken up into intermittent motions of regular form, providing equal periods between each motion, the moment of ending of one motion exactly coinciding with the moment of beginning of the next.

2 The number of these periods is counted

Continuous to Intermittent Motion

A device known as the "escapement" permits the escape of movements of the clockwork, each of the same duration This movement takes place in the train of gearwheels between the power source and the hands of the clock, so that by suitable gear ratios the turning of the wheels and the hands of the clock represents for the observer the Earth's rotation about the sun The escapement also provides the energy which keeps its own mechanism in rhythmic action Gould (1923) expounds the history and principles of chronometry

We find in the nervous system an exactly similar process, in which some *continuous* performance, such as movement or sensation, is transmitted by an *intermittent* process The example of nerve action-potentials serves to illustrate this point

Counting and Recording the Number of Escaped Cycles

The counting apparatus is provided by the passing of "hands" over the "face" of the clock, which provides, in its marked subdivisions, *intervals of space equivalent to intervals of time* Thus in the clock we have the equation of time with space Following this statement, we reach an exciting conclusion, for we find that

> Man, being equipped psychologically with a sense of space and a sense of time, may be considered physiologically as a clock system

Neurological Aspects of Chronometry and Navigation

The methods by which human beings relate themselves to their surroundings were outlined in previous papers (Gooddy and Reinhold 1952, 1953, Gooddy 1957a) The evolution of the neuroanatomical and neurophysiological techniques by which we are able to live purposefully in a three-dimensional environment was considered Suggestions of the importance of a fourth-dimension or time factor were outlined In the second paper (1953) the notion of "motion-sense" was introduced The breakdown of "motion-sense" in disease of the nervous system was illustrated by clinical tests of language, visual, auditory, and tactile perception, spatial judgments awareness of the significance of direction, constructional and navigational performance

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* From two lectures delivered at the University of California Medical Center, Los Angeles, Department of Physiology, November, 1957

The human faculty of finding one's way about (navigation), of realising the relations of parts of the body one to another, and of appreciating the interrelationships of objects of which one is only theoretically aware (e g, molecular structure of chemical compounds, geography, astronomy) has been developed for the needs of progress and survival to such a degree of perfection that these "functions" are relegated to subconscious level, except

1 In situations which are new (and therefore exceptionally difficult)—e g, finding one's way about in a strange place, especially in a foreign land without previous personal landmarks, and where the language is not understood There are then the equivalents of spatial disorientation and dysphasia Or in developing a new skill, such as touch-typing or the understanding of spherical trigonometry

2 In disease of the nervous system

In the papers mentioned above, it was also shown that the passage of time is essential for perception—that unless it is possible to say, for example, "I am not being pricked by a pin, I am being pricked by a pin, I am not being pricked by a pin" there can be no full or accurate description of the perception (and memory) of having been pricked by a pin

If the ideas so far expressed are accepted, we may make a statement of personal chronometry from clinical observations of personal navigation

Since (1) we are able to achieve personal navigation (spatial orientation), and since (2) the awareness of the passage of time is as essential for perception as the knowledge of the extensions of space, *we must be equipped with internal chronometric apparatus amenable to physiological analysis*

The Internal Clocks

We may now proceed to investigate the proposal that there are internal clock forms, which enable us to have a "sense of time", without using such external means as require the perception of a mechanical device

To prove that this proposal is true, it is necessary to show that there are systems or "mechanisms" in which are produced the exactly repeatable physical phenomena

The body does contain a large number of such "mechanisms", of which some are obvious and of special importance Others, of equal or greater importance, are less obvious The principle underlying their functions as clocks may be once more outlined *All that is necessary for a clock is "the detectable phenomena of accurate repetition"* The greater the accuracy of repetition, the greater the accuracy of the clock Extreme refinements of accuracy are provided from measurements of the motions of the *very large* or *very small* bodies The most accurate time measurements at present are derived from

1 The motions of the stars (bodies of immense size, remoteness, and speed of movement relative to the earth)

2 The vibrations of quartz crystals (100,000 oscillations per second)

3 The motions of the molecules of ammonia gas or cæsium (also showing striking contrast of size and speed compared with the earth)

That the human being through his body may have some "awareness" of molecular activity has been suggested (Gooddy and Reinhold 1953) We have, between our observations of the motions of heavenly bodies and the possible subconscious reckonings of molecular activities, the set of clocks now to be described It is to be noted at the outset that the patterns of clock mechanisms are so diverse that there should be a diversity of times recorded From this multiplicity of "times" may be derived the concept of "Time" that is, the average of physiological times is equivalent to "mean psychophysical time"

Physiological Clock Mechanisms

There are two main groups to be considered

1 The non-nervous organs and systems which have a rhythmic pattern of activity

2 The nervous mechanisms which transmit the impulses from which the action of non-nervous organs is detected Note —These nervous mechanisms themselves show rhythmic activity, which provides temporo-spatial patterns in the nervous system Such "dynamic patterns" may provide a link between physiologically demonstrable nervous activity and perception (Gooddy and Reinhold 1954, Gooddy 1956, 1957*a*)

Summary of non-nervous organs and systems showing rhythmic activity —There is some difficulty (artificiality) in defining this group, for every bodily structure is in some degree under nervous control, in that its activity is modified by action of the nervous system Such organs as the heart (which shows rhythmic activity of an obvious kind) ultimately depend on a number of local and general nervous (and neurochemical) mechanisms, from the branches of the bundle of His to the very complex cerebral modifying mechanisms (Gellhorn 1953) The heart-rate may vary from 40 to 160 beats a minute under cerebral influences Similarly the lungs, the bowel, the bladder, and the glands may vary in activity according to nervous activity

However, the point for present demonstration is that there are many bodily structures, not themselves nervous structures, which have *rhythmic activity* fulfilling the requirements of repetition necessary for a clock form We have also to consider those *rhythmic processes* (respiration, pulse, temperature, for example) which emerge as the most important consequences of the activity of rhythmically acting organs (heart, lungs)

Cardiovascular System
  Muscular activity
  Pulse transmission
  Nervous control
  Biochemical effects

Cerebrospinal-fluid System
  Two forms of pulse—cardiac and respiratory

Cardiorespiratory System
  Rhythmic neuromuscular activity controlling and controlled by biochemical adjustments in blood and tissue metabolism

Alimentary System
  Rhythmic activity of alimentary tube, from pharynx to rectum, associated with regular intake and output Glandular activity closely associated (e g, blood-sugar level)

Cardiorenal System
  Regulated output of soluble material in delicately adjusted volumes of fluid

Glandular and Autonomic Systems
  Growth, generation, gestation Regeneration Maintenance of standards, e g, metabolism, temperature Relation to mental states Healing Effect on size of body, development and age. Sexual cycles, male and female

From this rough classification, examples from the cardiovascular system may be used to provide illustrations

The Heart and Blood-vessels

The arterial pulse has, from antiquity, been noted for its generally regular rhythm under steady conditions The circumstances producing acceleration and deceleration to raised or lowered levels (tachycardia, bradycardia) or altered rhythm are common knowledge, popularly connected with the emotions Their description may be found in any textbook of medicine, cardiology, or pharmacology, as well as in works on psychology, and in poetry and non-medical prose, including the Bible There is, for any individual, an approximately steady rate—usually, during rest, between 65 and 75 beats a minute The average or "normal" pulse-rate is usually given as 72 a minute When Galileo in 1590 made his observation of the swinging lamps in the cathedral of Pisa, which led to his formulation of the principle of the pendulum (i e , that each swing of a freely suspended body takes the same time as any other, independently of its length or arc of swing) he is said to have used his pulse for a method of timing It says much for the detachment of scientific observation if at such a time of fundamental discovery Galileo's pulse remained steady

The physician detects the cardiac and arterial pulses by sight, touch, and hearing Technical devices are often used to magnify the fundamental rhythmic processes, which are associated with two distinct forms of appreciability

1 The local and distant effects of rhythmic contraction and expansion of muscular tissue (which may be detected in transmission either along the arterial wall or other tissues (heart apex-beat, abdominal aortic pusaltion), or felt by application of some part of the observer's body—usually the finger or palm)

2 The mechanical production of sounds, (*a*) by fluctuations of pressure in a valve-controlled tubular system, or (*b*) by muscular contraction directly In the first group we have the heart sounds in pairs, accompanying normal systole and diastole, the rumblings of abnormal confluences of blood, as in valvular disease of the heart (mitral stenosis in rheumatic heart-disease, or in arteriovenous communications (cerebral angioma) In the second group we have the accessory heart sounds

In health and daily life, we are not usually conscious of the heart's action, nor do we often make any form of analysis of it Nevertheless, the information is always available and is constantly presented to and by the nervous system, by the above-outlined methods, as well as in the well-established nervous channels leading directly from the organ The study of cardiovascular physiology and disease objectifies many of the details of the arterial pulse system

We find, therefore, that in the cardiovascular system there is a well-defined system of clocks Certainly this system is liable to frequent and considerable modifications of action leading to alterations in the time-values derived from the system However, over an extended period, such as a day or a week, a person will have a fairly steady average pulse-rate A person engaged in ordinary routine work of a sedentary type is likely to experience pulse-rates between, say, 65 and 85 a minute, with a mean value of about 72 a minute The brief periods in which he may be in a rage or frightened, or running for a bus, will be accompanied by an increased pulse-rate, but this peak-period, unless prolonged, will make little difference to the average over the twenty-four hours

In several conditions a high average pulse-rate may be maintained for long periods (anxiety, fever, thyrotoxicosis, heart-failure, paroxysmal tachycardia, intoxication) We have to ask ourselves whether such conditions are associated with alterations in some part of the time-sense It can be shown that such alteration does take place, though it is often unrecognised subjectively (i e , by the patient) until his health returns to normal, when he is able to have another (normal) time-sense to compare with the former

Rhythmic Activity in the Nervous System

We have now to consider what may be a new proposal about the nervous system and its activity The proposal is formulated thus

1 Because of its fundamentally rhythmic type of activity (associated with the "all-or-none" phenomena), at all neurophysiological levels,

2 Because the nervous system mediates sensory and motor activity, and thus is completely integrated with the reception and creation of rhythmic phenomena (e g , light and sound waves, habitual movements, such as walking, breathing),

3 Because the nervous system is the final mediator of the person's awareness of all the clock systems derived from rhythmic systems not primarily nervous,

4 Therefore the nervous system provides both the anatomical structure and the physiological activity essential for clock mechanisms, and *may be regarded as a clock*

If we accept the notion of the nervous system as a clock, we note immediately the complex nature of its structure The final clock, by which perhaps we say we "know about time", is the last abstraction of the innumerable subsidiary clock forms In neurophysiological terms, the alpha rhythm of the electroencephalogram shows the final abstraction from all other rhythms Rhythmic activity has been demonstrated in a single cortical cell (Phillips 1955)

Some important systems will now be briefly discussed

The Intrinsic Activity of Nervous Tissue

The basis of nervous activity is the transmission of the nerve impulse, which is the unit used by Eccles (1953) in his attempt to discover *The Neurophysiological Basis of Mind* The nerve impulse is used also by Katz (1952) as the fundamental unit of nervous activity Nerve-fibres have (*a*) rates of "firing," depending on the rate of stimulation and the refractory period, and (*b*) rates of transmission, depending on fibre cross-sectional area

Therefore, for habitual activity (whatever it may be) which we train ourselves to perform, there is a habitual rate of sensorimotor activity, which may be expressed in neurophysiological terms as habitual rates of firing and conduction along nerves This habitual rate of activity derived by abstraction from an infinity of activities, provides a very steady clock system at all levels, because of the reliability of "averaging" which is possible in a system composed of such immense numbers of units

The structure of the nervous system is well fitted to such a design for function, and differs from the cardiovascular system, which relies not on abstraction but on simple bulk transport (the blood-channels enlarging progressively towards the heart, which is conventionally regarded as the centre of the system) (Gooddy 1957b)

The Autonomic System

Inseparably linked with the clock systems classified as "non-nervous" is the autonomic nervous system, which traditionally holds a much neglected position in neurological study Only when the autonomic system is functioning normally can the individual make use of his *voluntary nervous system* *Only when the rates* of functioning of those metabolic systems which maintain life and health are normal does living matter (human being or plant or single cell) prosper

The autonomic system is the controlling device of innumerable neuro-anatomico-humoral systems, which are *set* in certain positions of adjustment according to the state of the individual These adjustments may be altered singly, or (in certain groups) totally They are so interconnected that it is not possible for one to be altered without an effect upon others, this relationship being the basic " mechanism " of homœostasis Simple examples may be seen in the chemico-neuro-chemical alteration of heart-rate during exercise, and the photo-chemico-neurological response of the pupil to light and shade Such adjustments are linked to change of state, and vary according to the degree of change (up to the limits of the system's performance if the limits are exceeded, pain and disability or disease result)

Thus we find that the autonomic system is compounded of many clock systems, which control (and are mutually controlled by) those " vegetative " processes essential for life The autonomic system provides the regularity of rhythms essential to volitional activity it is the nervous system of rhythmicity Its clock faces may be seen in countless forms Examples are shown in records of pulse, respiration, and temperature, in menstrual cycles, in uptake of radioactive isotopes, in photographs of a person in infancy, childhood, adolescence, maturity, old age When disordered in function, the autonomic system shows clock systems recording abnormally—in fever, pain, tachycardia, colic, and depression

These clock systems are neglected because we are over-familiar with their habitual perfection The *poet*, not the physiologist, knows this neglect, as an extract from A E Housman shows

" When I was off to dreamland
  And left my limbs forgot,
Who stayed at home to mind them
  And breathed when I did not ?"

The Special Senses and " Touch "

The special senses and touch provide a wealth of clock systems, which are to be discussed in detail elsewhere They depend for their clock-like activity on certain principles

1 They may be concerned directly in " reporting " from other clock systems, either specially designed and constructed to affect them—e g , the ordinary clock-face or watch-face (vision), and the chiming of clocks or the reception of verbal and electrical signals (hearing)—or naturally available in the world environment—e g , motions of stars, state of vegetation (vision), bird song, insect sound especially in tropics (natural auditory clocks are fewer than visual ones), ripeness, decay, perfection of cooking (taste and smell), arrival in harbour (balance), seasonal warmth or cold, ice, dust, drought (touch and thermal sense), passage of vehicles (vibration)

2 They provide information of external physical activity to which they are specially " tuned " The visual system distinguishes various *speeds* and *intensities* of light waves, the ear, various speeds and intensities of sound waves In so doing, sight and hearing provide the proof of their clock-likeness, because, for example, to distinguish between two musical notes, the auditory system has to differentiate rates of vibration *per second* (or any other time unit) Thus in music, pitch and " tune " are two obvious clock systems

The touch system is " tuned " to molecular activity (Gooddy and Reinhold 1953) as shown, for example, by our capacity to appreciate contact and distinguish differences of *hardness*

The " chemical " senses, smell and taste, provide judgments of rates of solubility and degrees of concentration

3 They *provide, without mechanical clocks*, each in its own modality, evidence of time passed and so the possibility of judging age The final perception of a modality is often expressed in time judgment " His face was so changed, he must have been in the last stages of his illness " (vision) " That engine is very ' rough ' it must be years since it was overhauled " (hearing) " That cheese is over-ripe " (smell) " This is the 1890 port " (taste) " That cloth was quite worn out " (touch)

4 They are concerned with order, or sequence The meaning of spoken and written words, and of mathematical symbols, and especially of musical notation, tunes, and harmony, depends on " navigation " of muscular and skeletal instruments (vocal apparatus, fingers, and pen) *Thus writing consists of a temporal* sequence of variously directed lines Phrases are meaningless without correct time sequence

5 They create some of the common units of nervous activity (nerve impulses) which, by their *temporal* as well as spatial patterns, provide a basis for perception (Gooddy 1957a)

The Locomotor Systems and Posterior Columns of the Spinal Cord

The locomotor system is here considered to consist of all the bodily apparatus necessary *for the directed movement of the limbs, the results* of which are known It is the custom, neurologically, to concentrate on the nervous control of muscles, and study " levels " of nervous activity It is equally or more profitable, from the point of view of function, to study the performance of limb segments about the joints which are their fulcra In such studies, we find, in the words of Descartes (*Dioptrique*) a " natural geometry ", which is of the greatest significance because it illustrates exactly, in ways capable of objective description and analysis, the principles of navigation and chronometry already outlined *This matter is to be described* with experimental elaboration elsewhere The points to be made here are

1 Movement is limited by the mechanical properties of joints, which are either of ball-and-socket or of hinge type Naturally we are able to derive compound movements by using the properties of many joints at once For example, in shaking hands there is a setting of the feet and a setting of the trunk upon the pelvis From the position of the hand at rest by the side, there is a slight forward movement of the shoulder-joint (20°) and a much larger movement of the elbow-joint (90°) There are also complex *angular adjustments of the* carpal, metacarpal, and phalangeal joints

2 *Space* traversed by a limb point depends on (*a*) the length of the limb segments and (*b*) the angular velocities of the limb segments about their joint axes

3 *Space* traversed will be deducible from the number of repeated joint movements, if counted

Points 2 and 3 will depend on the fact that

4 Each person has a habitual rate of movement (which can be varied at will, but usually lies closely about a mean value for the person)—e g , speech, walking, eating

We may conclude that *limb movements are clocks* of great importance and of general validity because there is general conformity of human size compared with distances covered Thus most adults are between 5 and 6 feet in height, and can easily manage to cover distances of several miles

The positions of the limb points are the hands of the locomotor clock upon the face of the earth

If there is a great difference of limb length (adult compared with child), and if the locomotor clock system is as important as has been proposed, there should be an appreciable difference of time sense between adults and children which we all know to be true.

Additionally, the larger limb is associated, over the same world distance, with a smaller angle of joint movement, and therefore a smaller angular velocity if the movement from one point to another occupies the same time as that taken by the shorter limb. The alterations of skin and muscle tension and the effects of the weight of the limb also provide "information" of clock-like type. We should not, therefore, be theoretically surprised if the nervous connections subserving the awareness of joint position, movement, muscle sense, and the motional aspects of cutaneous sensibility (touch) were found to be grouped together in the nervous system. (I do not conceal my astonishment at finding, by deduction from the foregoing hypothesis and not from textbook instruction, that the posterior columns of the spinal cord exactly fulfil these theoretical requirements.)

Brain-stem (including Cerebellum) and Thalamus

These regions are traditionally concerned with automatic arrangements to preserve the organism alive and provide the crude information for spatial orientation (especially "balance" and "sight"). The physiological relationships between the posterior-root components (which pass to either the posterior columns or the spinocerebellar (or spinothalamic) tracts) and the brain-stem nuclei and cerebellum are well known.

In providing the data for spatial orientation these regions must, ipso facto, provide temporal data.

In the thalamus are interrelated the sensory data from all forms of receptor, though we presume that at this "level", "discrimination" is impossible. We should expect to find with damage in this region a quantitative disorder of sensation, of a character differing from the qualitative defect found when the cerebral cortex is damaged. The reader may ask himself whether there is such a difference between thalamic symptoms and cortical symptoms. We know that with thalamic lesions there is a "raised threshold" (greater stimulation, an increased *rate*, necessary for detection) and "over-reaction" (pain, *very* painful, hot, *very* hot, pleasant warmth, *very* agreeably warm) and a delayed response.

Note on the basal ganglia.—We are told that the basal ganglia represent the evolutionary reptilian motor system, but we do not know their function in health. Lesions of this system result in alteration of muscle tone and the appearance of rhythmic involuntary movements. The tone defect is accompanied by a *slowing* of limb movement. The involuntary movements are characterised by their regular rhythmic nature. Tremor is a normal finding in healthy people; its rate is about 10 cycles a second. The tremor of anxiety and hyperthyroidism is an exaggerated form of the normal, at the same rate. In parkinsonism, the tremor is slower and coarser than normal. Both normal and abnormal tremors provide a clock system. Some patients with parkinsonism say that time seems to go faster since the onset of the disease, but others say it goes slower. The reasons for this are to be discussed elsewhere.

The Cerebral Cortex

It is generally agreed that those processes or faculties loosely classified under the titles of "memory", "foresight", "judgment", "intelligence", "behaviour", "concentration", "reasoning" are disordered in cases where we find evidence of damage to parts or the whole of the cerebral cortex.

Such processes, for all their apparent diversity, have one common underlying feature—namely, the loss of "timing". Thus when memory fails, we find a defect of recall and arrangement of time past. A failure of concentration is an inability to maintain a "fine-scale" sensorimotor activity ranged immediately about the present. Foresight, judgment and reasoning imply a failure of forward memory or "prediction". When these powers are lacking, it is easy to show that the patient can no longer estimate odds of probability concerning future events on the information available from the past. The patient, with a frontal-lobe tumour or cerebral atrophy, who is incontinent of fæces, has forgotten what it will be like, *in the future*, to have been incontinent. To say that "he does not *care* whether he is incontinent or not" describes accurately the circumstances, for if he were well, he would be horrified, because he recalls from the past that wilful incontinence signifies the breaking of social rules; and rules are formulated to direct future behaviour.

At a neurophysiological level we should expect to find evidence of clock systems, especially if it is accepted (*a*) that the cerebral cortex behaves in a calculator-like way and that "its function is to select, differentiate, condense and abstract rhythms or patterns of neuronal activity" (Gooddy and Reinhold 1954), and (*b*) that perception depends on the spatiotemporal arrangement of nervous activity.

We should be able to deduce, further, that the characteristic feature of the cortical neurophysiological clock should be a simplified rhythm, abstracted from the multitudes of nerve-cells, processes, channels, and impulses.

We see, in the electroencephalogram, the exact illustration of this deduction which (it is important to state) was derived from the hypothesis of this work and not from the admitted long-standing familiarity with the electroencephalograph. The electroencephalogram *is a neurophysiological demonstration at cortical level of the whole theory underlying this paper.*

Conclusions and Summary

This work presents an outline of a new hypothesis, derived from, and especially applicable to, study of the nervous system.

The instruments and discoveries of science are shown to be particular examples of mechanisms already perfected in living creatures. From this it follows that navigation and chronometry, demonstrated in the control of ships and aeroplanes, and the construction of clocks, are but the exteriorised examples of personal navigation and chronometry. We should, then, be able to detect and describe physiological chronometric mechanisms (clocks, clock systems) in the same way that spatial orientational mechanisms have already been described.

Clocks of non-nervous and nervous mechanisms are described. Examples of non-nervous clock-systems are given in a discussion of the rhythmic nature of the heart-beat.

The intrinsic rhythmic activity of the nervous system, in units and as a whole, is emphasised. Neurological clock-systems at various anatomical levels in the nervous system are described.

The electroencephalograph is used as evidence of the highly abstracted cerebral cortical clock-system, and as proof of the theory underlying this paper.

The work leads naturally to a study of disorders of the clock-system, which will form the subject of future communications

I am most grateful to the University of California, Los Angeles, for their generous hospitality, which enabled me to visit the Department of Physiology, and especially to Dr Robert D Tschirgi, associate professor of physiology, at whose invitation these lectures were given

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OCCULT INTESTINAL BLEEDING AS A CAUSE OF ANÆMIA IN ELDERLY PEOPLE *

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LATELY MEDICAL REGISTRAR †

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ANÆMIA is common in old people admitted to hospital, whatever their salient clinical condition, but is often revealed only by routine hæmatological investigation In the large majority of cases the anæmia is of the iron-deficiency type (Bedford 1952)

The importance of blood-loss in the production of iron-deficiency anæmia has been firmly established for younger age-groups (Moore 1955, *Lancet* 1955) but appears to be insufficiently appreciated as a major factor in anæmia of old age Thus, although Moore (1955) states that " nutrition plays a relatively minor role in the production of iron-deficiency anæmia among adults unless blood-loss also occurs ", Hobson and Blackburn (1953), in their survey of old people living at home, and the *British Medical Journal* (1955) state that iron-deficiency anæmia is due to dietary deficiency and intestinal malabsorption, and virtually dismiss the part played by blood-loss

We intend to show here that, whatever other factors are concerned, occult intestinal bleeding plays an important part in the pathogenesis of anæmia in old people

Material and Methods

The present study is based on 175 patients admitted consecutively to the geriatric unit, Cowley Road Hospital, Oxford Of these patients 19 were excluded either because they had overt bleeding or because they were aged less than 65 and therefore could not be held to be unequivocally elderly The remaining 156 patients with no overt bleeding and aged 65 or more comprised our material Of these 156 patients 61 (39%) were men and 95 (61%) women (table I) This preponderance of females merely reflects the usual preponderance of females over males in the sex ratio of patients admitted to this and similar hospitals All were under the care of one of us, and full clinical examinations were made of all by both of us independently

TABLE I—SEX-DISTRIBUTION OF ANÆMIA IN PATIENTS AGED 65 OR MORE ADMITTED TO HOSPITAL

—	Male	Female	Total
No of patients investigated	61 (39%)	95 (61%)	156
No of anæmic patients (Hb <80%)	25 (41%)	39 (41%)	64 (41%)

Weekly hæmoglobin estimations with the M R C grey wedge photometer (King et al 1948) and blood-film examinations were made on each patient Simultaneously a fresh specimen of fæces, obtained when necessary by digital manipulation per rectum, was examined for occult blood by the Gregersen test (Gregersen 1919) A hæmoglobin level of less than 80% (11 7 g per 100 ml) recorded for any patient at any time was arbitrarily taken to indicate anæmia, this being the same level as that chosen in the Sheffield survey (Hobson and Blackburn 1953) In anæmia as defined, " absolute values " for the mean corpuscular hæmoglobin concentration, the mean corpuscular volume, &c , were determined and, not routinely but in all cases where indicated for diagnosis, further investigation—e g , examination of the marrow—was made The tests for occult blood were recorded either as positive or negative, the former being limited to Gregersen's " strongly positive " reactions (Gregersen 1919), all other results being classed as negative Medicinal iron was not obligatorily withheld, and dietary restrictions were not imposed other than for therapeutic reasons

Results

Anæmia

Of the 156 patients 64 (41%) were anæmic as defined (table I), 34 (22%) having hæmoglobin levels below 75% and 21 (13%) below 70% (table II) More detailed examination of the blood, as described above, proved the anæmia to be of the iron-deficiency type in 60 (94%) of the 64 anæmic cases according to the generally accepted diagnostic criteria described by Whitby and Britton (1953), whatever else was present

Patients are grouped according to age in figs 1 and 2, which show that the incidence of anæmia was similar in all the age-groups over 65, such differences as were present are not significant The gross distribution (fig 1) reflects the number of admissions in each age-group, but, when anæmia is expressed as a percentage in each age-group (fig 2), the incidence is similar throughout the quinquennia over 65

The incidence of anæmia in the two sexes is equal—41% (table I)

These data thus clearly establish that iron-deficiency anæmia is common in patients aged 65 or more admitted to this hospital

Occult Intestinal Bleeding

Examination of the fæces of the 156 patients for occult blood showed positive reactions in 85 patients (55%)

TABLE II—INCIDENCE OF ANÆMIA IN 156 PATIENTS AGED 65 OR MORE ADMITTED TO HOSPITAL

Hb level	No of patients
<80%	64 (41%)
<75%	34 (22%)
<70%	21 (13%)

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* The basis of a communication to the Medical Society for the Care of the Elderly, Manchester, in October, 1956

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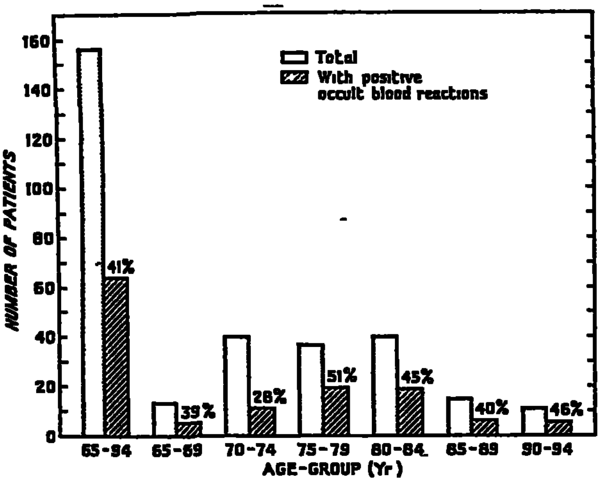

Fig 1—Age-distribution of anæmia

(table III) When the patients are grouped according to age, and the gross distribution (fig 3) is corrected by expression as a percentage (fig 4), the incidence of positive reactions for occult blood is similar in all the age-groups over 65, such differences as are present are not significant

These data thus clearly establish that positive occult-blood reactions are common in patients aged 65 or more admitted to this hospital

Technique of test for occult blood in fæces—For each test a smear of a fresh specimen of fæces is made on a clean new glass slide and viewed against a background of white paper A powder containing a mixture of 25 mg of benzidine hydrochloride and 200 mg of barium peroxide ‡ is dissolved in 5 ml of glacial acetic acid by shaking in a test-tube (the resultant solution thus contains 0 5% of benzidine HCl) The fresh solution of benzidine is poured at once over the fæcal smear A deep blue colour appearing within 15 seconds is the only positive result A blue or a green colour appearing within 30 seconds—Gregersen's (1919) ' weakly positive' result—and no colour, or any colour appearing after 30 seconds are all negative results In this study only the appearance of an immediate blue colour—i e, within 15 seconds—was classed as positive Delayed colour reactions were classed with no colour, as negative Gregersen (1919) accepted all three colour reactions as positives , whereas we followed Needham and Simpson (1952) in limiting our interpretation of positive reactions " as indicated above.

Relationship between Anæmia and Occult Intestinal Bleeding

Of the 64 anæmic patients as defined (anæmic group) 50 (78%) gave positive reactions for occult blood in the stools (table III), whereas of the 92 cases with hæmoglobin more than 80% (non-anæmic group) only 35 (38%) gave a positive reaction on testing for occult blood (table III) This difference is statistically highly significant ($\chi^2 = 24\ 46$, $n = 1$, $P = < 0\ 01$)

These data thus clearly indicate that, in elderly patients admitted to this hospital, anæmia and positive occult-blood reactions are related

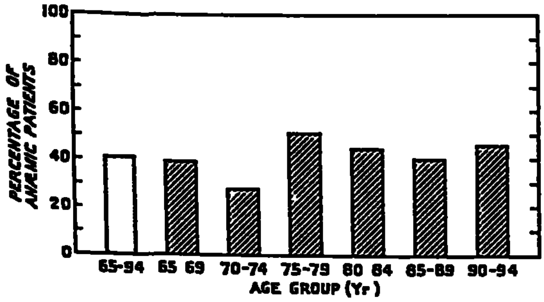

Fig 2—Age-distribution of anæmia.

Validity of Definition of Anæmia

Several published statistics of "normal values" for hæmoglobin levels in elderly people include figures of less than 80% (Wintrobe 1933, Medical Research Council 1945, Olbrich 1947, Shapleigh et al 1952), but it is highly probable that these so-called "normal values" include in their lower ranges figures derived from patients who had hæmorrhage or other blood diseases The fact that the mean "normal values" for postmenopausal women are lower in all the series than those for men also indicates a pathological basis because menstrual loss no longer applies The view of Shapleigh et al (1952) appears to be amply justified

> " the range of minimum and maximal values (i e of hæmoglobin level in old people) is greater than that usually seen in younger age groups which suggests that subjects were included who had diseases other than those common to the ageing process "

Olbrich (1947) similarly states

> " some of the reported figures are so far removed from the ' normal ' as to raise the suspicion that they refer not to the physiologically aged but to patients suffering in old age from a variety of pathological conditions "

Validity of Gregersen's Test for Occult Blood

Gregersen's (1919) test is a modification of the benzidine test (Adler and Adler 1904) A positive result, as defined above, indicates occult intestinal bleeding in virtually all cases, provided that liver and black pudding are excluded from the diet Neither medicinal iron administered orally nor any article of diet other than liver and black pudding (which contain much blood) affects the result. At least 3 ml of blood must be ingested to produce a positive result

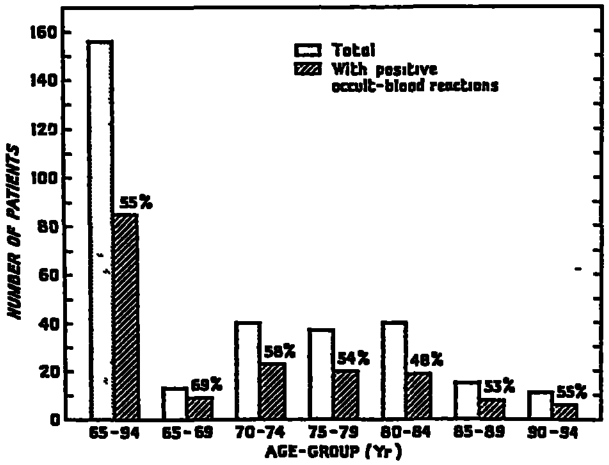

Fig 3—Age-distribution of positive occult-blood reactions

Needham and Simpson (1952), who used this test on 603 unselected outpatients on entirely unrestricted diets, found a source of gastrointestinal bleeding in 88% of all cases with positive reactions for occult blood in the stools

Forshaw and Mason (1954), by allowing three days to elapse after liver had been eaten before they examined the stools for occult blood, reduced the number of unexplained (false) positive results to 1% Since, however, elderly patients are commonly constipated, Forshaw and Mason's modification of the test does not materially improve the results in the older age-groups

No dietary restrictions were imposed on our patients Though an indefinite (but certainly small) number in

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‡ Boxes of this powder were obtained from Messrs Allen & Hanburys Ltd., but, we understand, are no longer available

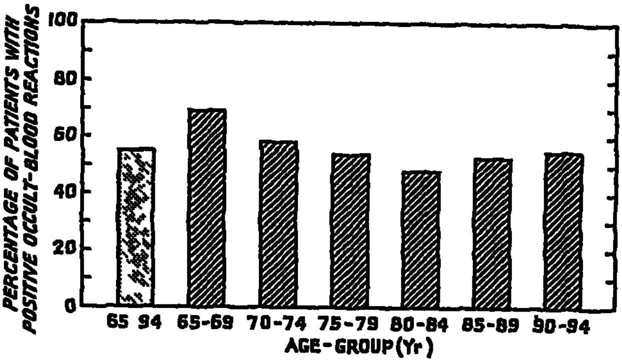

Fig 4—Age-distribution of positive occult-blood reactions.

both the anæmic and the non-anæmic groups may have given a false positive reaction for occult blood in the stools due to ingested liver, it is equally true for both groups (none had eaten black pudding, which is not a popular article of diet in and around Oxford) .Since the ingestion of liver in neither group of patients was in any way selective, and since there was no greater incidence of constipation in either group, the conclusion that the incidence of occult intestinal hæmorrhage was greater in the anæmic than the non-anæmic group to a highly significant degree is therefore valid, provided that the validity of Gregersen's test is accepted For the reasons given above, and for those that follow, we consider this to be the case, and we have therefore used the terms "positive reaction for occult blood" and "occult intestinal bleeding" synonymously

TABLE III—INCIDENCE OF OCCULT INTESTINAL BLEEDING IN ANÆMIC AND IN NON-ANÆMIC PATIENTS

—	No of patients investigated	No of patients with occult bleeding
Anæmic	64	50 (78%)
Non-anæmic	92	35 (38%)
Total	156	85 (55%)

Though we strongly affirm the validity of Gregersen's test (upon which our thesis largely rests) we are fully aware that many workers doubt its reliability, and it is therefore necessary to adduce further supporting evidence

At first sight the substantial number (38%) of patients in our non-anæmic group who gave positive reactions for occult blood in the stools appears to provide a contrary case We have admitted that an indefinite but certainly small number of these patients may have given a false positive occult-blood reaction due to ingested liver Long surveillance of these patients has, however, provided irrefutable supporting evidence because, although some died without or before becoming anæmic, most of them developed anæmia within two years, and only 4% remain in whom we have not yet been able to demonstrate an anæmic phase It must be emphasised also that our thesis is not that all who bleed from the gastrointestinal tract necessarily are or become anæmic—nor is this to be expected—but the contrary—i e, that the vast majority of anæmic patients admitted to this hospital show evidence of blood-loss from the gastrointestinal tract (that the blood-loss is an important factor in the pathogenesis of their anæmia is a logical corollary)

Although blood and fæces were examined simultaneously, anæmia and positive occult-blood tests did not necessarily coincide Indeed the positive occult-blood reactions often preceded the development of anæmia by some weeks, and in many cases there was no apparent time-relationship between them—and this too is not surprising Of paramount significance are the facts that almost all anæmic patients who lived long enough showed positive reactions sooner or later for occult blood in the stools, and that all patients with persistently positive Gregersen tests sooner or later, if they lived long enough, developed anæmia

All these reasons lead us to believe that Gregersen's test, when properly performed, is reliable, and that allegations to the contrary arise largely from neglecting the importance of fresh reagents, misinterpretation and lack of standardisation of results, and improper collection, storage, and preparation of fæcal specimens for the test Therefore we did not check our results by other methods, moreover all the established older tests are of very much more questionable validity, and those more recently introduced—e g, the o-tolidine and radioactive-isotope methods—have not yet been validated as regards diet, they are still being standardised against the Gregersen test and so would not have affected our results (Kohn and O'Kelly 1955, 1958, Ogilvie 1957) Nevertheless Gregersen's test will certainly be superseded—not because it is unreliable but because many unjustifiably believe it to be so, because it is undoubtedly cumbersome and tedious to perform, and because the carcinogenic potentiality of benzidine has given rise to so much alarm that benzidine has become virtually unobtainable and almost no pharmacist can be found who will handle it

The most promising of the newer methods is a slide technique using o-tolidine, but current experiments (P D Bedford and M M Weeks, in preparation) are showing that a tablet test using o-tolidine and fæcal suspensions is both convenient and simple in operation and promises to yield results as reliable as those obtained by Gregersen's method

Discussion

In the present series 41% of patients aged 65 or more admitted to hospital were anæmic at a hæmoglobin level of less than 80%, and 13% had a level of less than 70% Monroe's (1951) figures relate to 7926 unselected hospital patients aged more than 60 with "secondary anæmia" due to blood-loss and inadequate production (marrow hypoplasia) and are thus not strictly comparable, but the incidence of anæmia at a hæmoglobin level of less than 70% in Monroe's series is in substantial agreement with our own at the same hæmoglobin level—namely, 16% and 13% respectively

Hobson and Blackburn (1953), in their Sheffield survey, found the incidence of anæmia at a hæmoglobin level of less than 80% in old people living in their own homes to be much lower (5 1% of men and 6 5% of women, 6% of the total) compared with 41% in the present series The high incidence of iron deficiency (84%) in their anæmic cases is, however, in line with our finding of 94% Hobson and Blackburn state, referring in particular to Monroe's (1951) figures, " the idea that old people are anæmic may have arisen from hospital experience " The present series and the Sheffield survey are comparable as regards age and sex, and, though the conclusions of Hobson and Blackburn are undoubtedly substantially true, we feel that the discrepancy is not entirely explicable in terms of "hospital selection" of cases or of geographical differences, although either or both of these factors may be, and probably are, significant We feel that, if the hæmoglobin had been estimated more often in every patient in the Sheffield series, a much higher incidence of anæmia might have been revealed, because it is our experience that, over weeks or months, anæmia may be manifest only intermittently and can be discovered only by frequent serial estimations of hæmoglobin

The important studies on iron metabolism summarised by Moore (1955) show unequivocally that blood-loss is the principal factor in the pathogenesis of iron-deficiency anæmia

It has been shown with little room for doubt that dietary (nutritional) and intestinal-absorption defects do not by themselves—i.e, without blood-loss—play a major part in the production of iron-deficiency anæmia, and that, even when iron is completely absent from the diet, it would require many years for anæmia to develop, provided there was no concomitant blood-loss It has been shown too that achlorhydria, which increases in frequency with age (Bloomfield and Polland 1933), is not a significant factor (Moore 1955) Blood-loss, however, which is often intermittent and difficult to detect, is of primary importance, and, when there is such blood-loss, nutritional factors play a contributory part in the pathogenesis of iron-deficiency anæmia In these circumstances the role of ascorbic acid, which promotes the absorption of iron from the intestine in healthy people and even more in those who are iron-deficient (Moore 1955, *Lancet* 1955), is particularly significant The ascorbic-acid content of the diet of many elderly people is often deficient (Pyke et al 1947), especially in those who live alone, and this deficiency, together with a low dietary intake of iron, is without doubt of considerable contributory, but subsidiary, importance to the factor of blood-loss in the anæmia of old age

Another and common contributory factor which we feel has been insufficiently taken into account is the poor dietary intake of protein of many elderly people (Ohlsen et al 1948, 1950, 1952), which, together with the protein lost in the hæmoglobin by repeated hæmorrhage (Robscheit-Robbins and Whipple 1949, Whipple and Robscheit-Robbins 1951), may lead to iron-deficiency anæmia in elderly people through protein depletion Support would be lent to this theory both by our own frequent demonstration of hypoproteinæmia in elderly people admitted to hospital (P D Bedford, unpublished observations) and (admittedly by analogy) by Woodruff's (1955) observation in African natives, of anæmia which was associated with hypoproteinæmia and was corrected by increasing the dietary intake of protein alone

Neither hypoplasia of erythropoietic tissues nor primary deficiencies in intestinal absorption of iron (including the steatorrhœas, which are rare in elderly people) are considered here, because they are not germane to this discussion

Conclusions

Our conclusions about iron-deficiency anæmia in elderly people are in complete accord with those of Moore (1955), who states

> “ although theoretically poor diets or absorptive defects may cause iron-deficiency over many years on a nutritional basis it is far more likely that the cause is undetected loss (of blood) This loss may be slight or intermittent and may have to be diligently searched for It may take weeks or months until one can eventually demonstrate (that) occult hæmorrhage (is taking place) ”

The causes of occult intestinal blood-loss are, of course, many and various (ranging from peptic ulcer to uræmia), but it is not our purpose here to discuss the role of each in the pathogenesis of anæmia in elderly people or to assess the contributory role of such factors as hypoplasia of the bone-marrow

It is firmly our view that anæmia is common in elderly people, and that the concept of a physiological anæmia of old age is entirely erroneous It follows axiomatically that, in all such cases, full and detailed inquiry should be made into the cause of the anæmia and particularly into the source of any blood-loss §

Summary

Of 175 patients consecutively admitted to the geriatric unit, Cowley Road Hospital, Oxford, 156 aged 65 or more with no overt hæmorrhage were studied

Of these 156 otherwise unselected patients 64 (41%) were anæmic, with hæmoglobin levels of less than 80% (11 7 g per 100 ml), the anæmia in the large majority of cases being of the iron-deficiency type

Evidence of occult intestinal hæmorrhage was more than twice as common in the anæmic patients than in the non-anæmic, this difference is statistically highly significant and indicates a direct causal relationship between anæmia and occult intestinal hæmorrhage in the patients studied

It is concluded that anæmia is common in the elderly, and that, whatever other factors may be concerned, occult intestinal bleeding plays an important part in the pathogenesis of anæmia in old people

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THE NATURAL HISTORY OF CHRONIC BRONCHITIS

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COMMENDING the detailed recording of the evolution of chronic disease, Sir William Gull said “ In disease, one stream of morbid action naturally falls into another, and, whilst morbid anatomy gives us the final synthesis of results, there is but one possible means of analysis, and that by noting beginnings, order and progress ”

In the study of the natural history of chronic disease, the retrospective history of the already disabled patient is subject to the vagaries of human memory The sickness-absence records of a stable occupational group, on the other hand, have the merit of accuracy in timing the onset, duration, and sequence of disability from both major and minor illness arising during the working life, and, to some extent, this compensates for the poverty of clinical detail This paper describes how such records may supplement ordinary clinical studies by relating the frequency, timing, and character of respiratory and other illnesses among men doing the same job but in different environments to the development of chronic bronchitis

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§ Our self-imposed axiom was of course applied, but we have deliberately omitted all ætiological data and discussion to avoid the possibility of deflecting attention from our single thesis However, it can be briefly stated here that 64% of the anæmic patients had organic lesions and in the remaining 36% no cause was found

Material and Method

The Treasury Medical Service advises the Post Office and other Government Departments on the health of their employees, and gives reasonably uniform advice on the clinical aspects of retirement on grounds of ill health throughout the United Kingdom At the time of such invaliding, the man's record of sickness absence during his Civil Service career is carefully reviewed In this study we have used the records of 565 postmen retired prematurely because of chronic bronchitis, and of 45 postmen who died in the service from that cause, during the period 1950–54 inclusive The subsequent fate of 517 of the invalided men who were entitled to pensions was investigated early in 1957 by the Post Office department concerned The 517 pensioners were followed up in this way for periods of up to seven years varying with the date of retirement, and of these men only 17 (3%) could not be traced The certified cause of death was obtained either from official records or at the General Register Office for 90% of the 124 who died during the follow-up period

The interpretation of the sickness pattern in men ultimately disabled or dead from bronchitis requires comparison with men not thus affected " Controls " were therefore randomly selected from among postmen who were still actively employed in the same office at the time of the " bronchitic's " death or retirement and who matched him as closely as practicable in age and length of service The Post Office furnished complete sickness-absence records both for the " bronchitics " and for these corresponding " control " individuals

Analysis of the data entailed a comparison of the sickness history at different ages of " bronchitics " and " controls " and a study of the coincidence of this disease with others, whether respiratory or not, in the same individual A recent survey (Fairbairn and Reid 1958) has shown that, of the more readily measurable aspects of the local environment, fog frequency is specifically related to the incidence of disablement and death from severe bronchitis For that reason we have compared the nature, progress, and prognosis of bronchitis among postmen working in areas where contrasts in fogginess imply different exposure to polluted air

Results

In table I are compared the incidence and duration of attacks of bronchitis at different ages in bronchitic postmen and their fit colleagues At all ages the men who were ultimately disabled or who died in the service had more and longer absences from bronchitis, and the excess increases absolutely and relatively after the age of 45 The average age at the first recorded attack of bronchitis is 44, and complete disablement or death in service ensued at the mean ages of 54 and 56 respectively

As table I implies, the study of the natural history of a chronic disease such as bronchitis requires long-term records The analysis has therefore been concentrated on 448 postmen for whom adequate controls were available, and for whom sickness records could be found covering service before the age of 45 and whose survival status at the end of follow-up was known 146 such postmen (33%) died either in service or in the follow-up period

TABLE I—INCIDENCE AND DURATION OF ATTACKS OF BRONCHITIS AMONG " BRONCHITICS " AND " CONTROLS "

Age (yr)	Attacks of bronchitis per 1000 man-years		Average duration of attacks (*days*)	
	Bronchitics	Controls	Bronchitics	Controls
15–	122	13	12 8	2 8
25–	145	54	12 7	7 3
35–	254	64	17 1	11 2
45–	736	101	23 0	14 9
55–59	1275	129	40 6	18 7

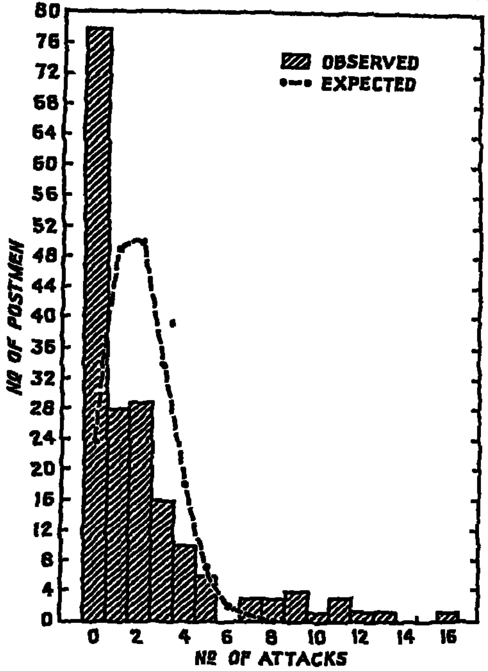

Fig 1—Distribution of no of attacks of bronchitis per person in "bronchitic" postmen aged 35–44, compared with expectation based on equal susceptibility

INDIVIDUAL PREDISPOSITION TO RESPIRATORY DISEASE

The excess in bronchitis morbidity in earlier life raises the question of individual susceptibility This can be further studied by setting out, as in fig 1, the distribution of the number of attacks per person among those bronchitic postmen whose records were available for the whole of their service between the ages of 35 and 44 inclusive This observed distribution can be compared with expectation based on the Poisson law of chance behaviour, which assumes similar exposure and equal susceptibility for every individual There is a clear suggestion that not all the bronchitics were equally susceptible, and that, in fact, the overall excess in frequency over the " control " level seen in fig 1 may come partly from the adverse experience of a " bronchitis-prone " minority As table II shows, this minority of men with a more than average number of attacks of bronchitis early in middle life have nine times as many recorded attacks of asthma—an excess which emphasises the allergic component of their sickness history But they also have more absences from other respiratory infections and from other causes of absence There is thus some general tendency to incur absence from work, but the seriousness of their disability is obvious in the fact that 20% of these men are known to have died either in the service or within seven years of retirement

TABLE II—INCIDENCE OF RESPIRATORY AND OTHER DISORDERS IN " BRONCHITICS " WITH DIFFERING BRONCHITIC HISTORIES UNDER THE AGE OF 45 (ATTACKS PER 1000 MAN-YEARS UNDER 45)

Disorder	No of attacks of bronchitis under age 45	
	More than average	Less than average
Upper respiratory illness	624	457
Asthma	56	6
Pneumonia	7	4
Pleurisy	10	7
All other illness	1134	822

ASSOCIATED RESPIRATORY AND CIRCULATORY DISEASE

The disparity in sickness experience between "bronchitics" and "controls", in table I, is greatest after the age of 45. Table III shows the contrast in attack-rates after that age between postmen who had been retired because of bronchitis and were alive at last follow-up, those who had died, and the matched controls for each group. Attacks of bronchitis and of asthma are 8–10 times more frequent in both groups of bronchitics than in presumably healthy men of the same age working in the same conditions. There is also a significant excess over the control level in both groups in the frequency of upper-respiratory infections. Circulatory disorders, usually described as "myocarditis" or "hypertension" by the certifying physicians, are likewise much more frequent in both bronchitis groups. The particularly high incidence among those who died prematurely indicates the prognostic importance of such diagnostic labels. Pneumonia and pleurisy are much commoner, as table III shows, among the bronchitics than among the controls, but the difference between "dead" and "survivors" at follow-up is small. Indeed, sickness histories of the dead appear to be distinguished more by the frequency of cardiovascular disorders than of other diseases of the chest.

TABLE III—FREQUENCY OF BRONCHITIS AND RELATED DISEASE AMONG "BRONCHITICS" AND "CONTROLS" (ATTACKS PER 1000 MAN-YEARS OF EXPOSURE OVER 45)

Diagnosis	Bronchitic survivors	Controls	Bronchitic deaths	Controls
Bronchitis	914	115	815	82
Upper respiratory	539	321	471	359
Asthma	56	6	56	5
All heart disorder, including hypertension	28	5	54	2
Pneumonia	10	2	14	2
Pleurisy	17	6	17	3

TABLE IV—PNEUMONIA AND/OR PLEURISY PRECEDING THE FIRST ATTACK OF BRONCHITIS IN "BRONCHITICS" ACCORDING TO STATUS AT FOLLOW-UP

Population	Status at follow-up			Case-fatality rate (%)
	Survival	Death	Total	
No. of "bronchitics"	302	146	448	—
No. of cases where				
Pneumonia preceded bronchitis	8	4	12	33
Pleurisy preceded bronchitis	15	9	24	38
Pneumonia or pleurisy preceded bronchitis	20	12	32	38

Rather surprisingly, pneumonia and pleurisy appear in table IV to precede repeated attacks of bronchitis fairly seldom—in only 32 out of 448 cases (7·1%) was either condition the first major respiratory illness recorded. The ultimate fatality-rate in these 32 cases is at 38% little different from 32% in the remaining cases.

The experience after the age of 45 of the two groups of bronchitics in respect of other disease categories is set out in table V. Clearly, although those whose death is recorded in the service or at follow-up differ little from their controls, the invalids who survive have consistently more absences than the corresponding controls. This disparity in absence from other diseases, which is much less than that noted for bronchitis, no doubt reflects the psychological factors affecting a minority of the less seriously ill men.

OTHER ASSOCIATED DISEASES

Table VI shows the experience of peptic ulceration in "bronchitics" and "controls" compared with expectations based on the age-specific incidence-rates derived from a field survey of peptic ulceration in other occupational groups in Britain (Medical Research Council 1951). For the "controls", the observed number of cases is just within the chance limits of the expected value, among the "bronchitics" twice as many men had peptic ulcer as expected—a significant excess.

TABLE V—FREQUENCY OF NON-RESPIRATORY ILLNESSES AMONG "BRONCHITICS" AND "CONTROLS"

Diagnosis	"Bronchitic survivors"	"Controls"	"Bronchitic deaths"	"Controls"
Rheumatic	216	122	123	122
Gastrointestinal	102	75	77	56
Skin	63	37	37	54
All other	915	556	731	639

The incidence of other serious diseases can be further studied in the distribution of the cause of death given by the attending practitioner for the 113 deaths among the 500 pensioners successfully followed up after discharge. To the total man-years of exposure throughout the period of follow-up for the 500 men were applied the death-rates in England and Wales by cause for males aged 50–59 in 1952, the middle year of the period. The results of comparing observation with expectation on this basis are given in table VII. Deaths from bronchitis and other respiratory causes are, of course, grossly excessive, but the number of deaths from non-pulmonary cancer (6) agrees quite closely with the number expected at national death-rates (4). Even with 10% of all deaths unallocated, lung-cancer deaths observed (12), on the other hand, are significantly more than might have been expected at these standard rates (3). Similarly, deaths certified as due to coronary disease are significantly more than the expected numbers.

TABLE VI—NUMBERS OF MEN WITH RECORDED HISTORY OF PEPTIC ULCERATION IN "BRONCHITICS" AND "CONTROLS" (COMPARED WITH THAT EXPECTED AT AGE-SPECIFIC INCIDENCE-RATES DERIVED FROM A MEDICAL RESEARCH COUNCIL SURVEY)

—	"Bronchitics"	"Controls"
Recorded	60	46
Expected	30	36

ATMOSPHERIC CONDITIONS AND ONSET OF BRONCHITIC ATTACKS

The short-term variation in the health of chronic bronchitics implies a sensitivity to atmospheric changes. There is some disagreement, however, about the relative effects of cold and humidity, particularly during fog, and of the chemical pollutants which inevitably pervade the urban fog.

TABLE VII—CERTIFIED CAUSE OF DEATH AT FOLLOW-UP IN POSTMEN INVALIDED FROM BRONCHITIS, COMPARED WITH THAT EXPECTED AT GENERAL MALE DEATH-RATES FOR 1953 AT AGES 50–59

Cause of death	No. of deaths	
	Observed	Expected
Bronchitis	51	2
Other respiratory	11	1
Cardiovascular		
Coronary disease	13	5
Other	10	3
Cancer		
Lung and respiratory	12	3
Other sites	6	4
Pulmonary tuberculosis	1	1
Central nervous system	6	2
Digestive	2	1
Other	1	3

In the 1939–45 war, records of fog frequency in the London area were regularly maintained Among the bronchitic postmen included in the survey, 103 worked in that area during the period 1941–46 It was thus possible to compare monthly trends in the incidence of absence from work due to bronchitis with contemporary levels in temperature, humidity, and presumptive air pollution during fogs which decreased visibility to below the arbitrary standard range of 1100 yards The relation of the environmental factors to the frequency of onset of bronchitis attacks can be most readily summarised by averaging the values in each month of the year over the six-year period Fig 2 shows the results of this condensation of the data on a logarithmic grid which clarifies the relative changes in the variables from month to month

Temperature (here displayed in inverse form as 1/°F), fog, and bronchitis frequency are clearly all related, but, although the incidence of bronchitis rises with the autumnal fall in temperature, the subsequent month-to-month changes in incidence are more closely related to changing fog frequency and thus, in a built-up area such as London, to the associated air pollution

PROLONGED EXPOSURE TO AIR POLLUTION AND EVOLUTION OF CHRONIC BRONCHITIS

The immediate effects of exposure to peak concentrations of air pollutants may thus be obvious, but the long-term results are still obscure The natural history of bronchitis can be usefully compared in *four groupings* of areas in the United Kingdom, with nearly equal postmen populations, arranged in order of the frequency there of fairly dense and presumably polluted fog Table VIII shows the trends in attack-rates among bronchitic postmen in these four areas at different ages At the youngest ages there is little difference between the areas, but over the age of 45 the disparity between lightly polluted and heavily polluted areas becomes obvious

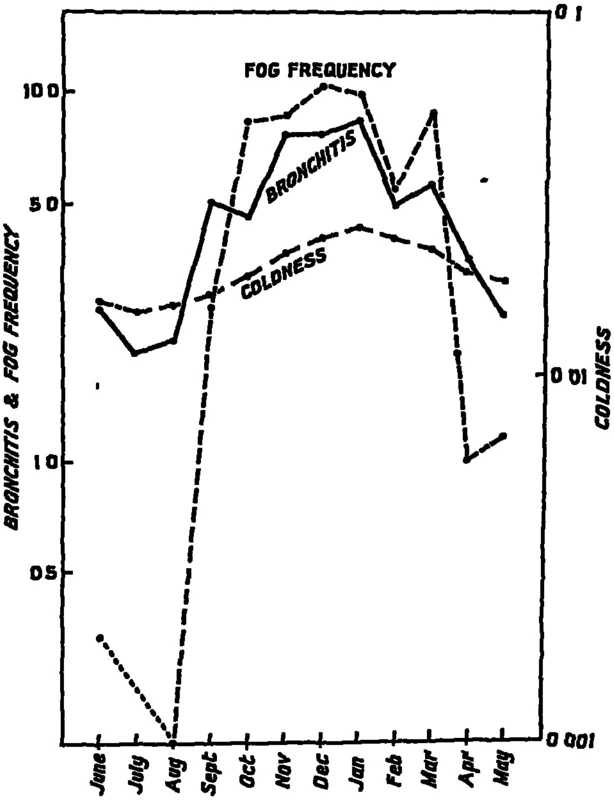

Fig 2—Local environment and onset of bronchitis in "bronchitic" London postmen (average of mean monthly values 1941–46 shown on logarithmic scale)

Bronchitis=attacks per 100 man-months
Coldness=reciprocal of mean monthly temperature (°F)
Fog frequency=average number of days per month with visibility less than 1100 yards
No foggy days occurred in July in 1941–46

TABLE VIII—AGE-TRENDS IN SICKNESS ABSENCE FROM BRONCHITIS IN "BRONCHITIC" POSTMEN IN FOUR GROUPS OF AREAS WITH INCREASING PRESUMPTIVE AIR POLLUTION (ATTACK-RATE PER 1000 MAN YEARS)

Age (yr)	Pollution group			
	I	II	III	IV
25–	184	120	143	119
35–	243	200	298	251
45–	568	579	748	967
55–59	1069	1126	1259	1563

The end-result of local conditions may be more apparent in the mortality of "bronchitic" postmen either while still in the service or after invaliding Table IX shows the proportion of all "bronchitic" postmen who die from the disease or its complications while still in the service. This goes up from 3% in the least foggy to 11% in the most foggy areas of the country

TABLE IX—DEATHS IN THE SERVICE, AND TOTAL DEATHS AND RETIREMENTS FROM BRONCHITIS IN POSTMEN, IN FOUR GROUPS OF AREAS WITH INCREASING PRESUMPTIVE AIR POLLUTION

Pollution group	Deaths in service	All deaths and retirements	Rate (%)
I	4	126	3
II	8	138	6
III	16	195	8
IV	17	151	11

Among those who are retired on pension, the proportions surviving at each year thereafter in the less heavily and more heavily polluted areas can be seen in the life-table statement of survivorship given in table X At the end of the seventh year of follow-up, 36% of the original group in the less affected regions are likely to have died, but 44% will have died in the more foggy areas The seriousness of the disease and the aggravating effect of atmospheric conditions are thus obvious The nature of this aggravation is apparent in table XI, which shows the greater incidence of pneumonia, pleurisy, and heart disorder in the more fog-ridden parts of the country in the critical age-group of 45–54 The high wastage from bronchitis in this age-group in both areas leaves male residual populations of bronchitics who differ little in the frequency of complications

TABLE X—PROGNOSIS IN POSTMEN INVALIDED OWING TO CHRONIC BRONCHITIS EXPECTED NUMBERS OF SURVIVORS UP TO SEVEN YEARS FROM THE TIME OF INVALIDING IN THE MORE POLLUTED AND LESS POLLUTED AREAS OF THE UNITED KINGDOM

Years after invaliding	Pollution groups	
	I and II	III and IV
0	1000	1000
1	946	911
2	871	868
3	823	797
4	779	763
5	742	687
6	723	613
7th yr	641	555

Discussion

In the study of the natural history of a chronic disease we are looking for evidence of personal and environmental factors which favour its onset or evolution and for illnesses which aggravate its course or point to a common origin

The effect of epidemics of upper-respiratory infection on bronchitis mortality has already been suggested by the similar fluctuations in total sickness absence, which are largely due to its respiratory component, and the annual death-rates from bronchitis (Reid 1956) At all ages postmen who are ultimately disabled or die because of bronchitis do have far more frequent absences from upper-respiratory infections, asthma, pleurisy, and pneumonia than their fitter colleagues working in the same conditions On the other hand, pneumonia and pleurisy are relatively seldom the precursors of a series of repeated attacks of bronchitis, and cases beginning in this way have much the same prognosis as the others The finding that sickness histories of those who died within the period of review were distinguished more by excessive frequency of circulatory disorder than by a high incidence of pleurisy and pneumonia is more consistent with Fulton's (1953) emphasis on the frequency of such complications than with views such as those of Parkinson and Hoyle (1937) that congestive heart-failure was seldom the result of chronic lung disease

TABLE XI—INCIDENCE OF CARDIOVASCULAR AND PULMONARY COMPLICATIONS IN BRONCHITIC INVALIDS IN AREAS OF DIFFERING POLLUTION (ATTACK-RATES PER 1000 MAN-YEARS)

Age (yr)	Group I and II	Group III and IV
All heart and hypertension		
25-	4	0
35-	4	3
45-	14	29
55-59	89	80
Pleurisy and pneumonia		
25-	16	18
35-	12	14
45-	21	27
55-59	48	45
Total		
25-	20	18
35-	16	17
45-	36	56
55-59	137	125

These disagreements between physicians practising in different parts of the country may be explained by the evidence from this study of the effect of regional differences in air pollution on respiratory morbidity The importance of environment to disease evolution is clearly implied by the contrasting sickness and mortality experience of bronchitic postmen in parts of the country with different levels of presumptive air pollution Not only are postmen more frequently disabled by, or die from, bronchitis in the more heavily polluted areas (Fairbairn and Reid 1958), but there is some indication that the character of the illness differs It seems that after the age of 45 the severity of these respiratory illnesses is increased by the atmospheric conditions, while grave chest infections and circulatory embarrassment cause large increases in both the immediate and long-term fatality-rates The acute effects of foggy conditions emerge from the coincidence of onset of bronchitic attacks with thick fog rather than of cold and humidity—a finding from sickness records which corresponds to the more detailed clinical records of the association produced by Waller and Lawther (1957)

Although the role of atmospheric pollution in precipitating and aggravating bronchitis may thus be evident, the personal factors involved are still obscure An undue susceptibility to absence before the age of 45 because of respiratory disease seems to be characteristic of a minority of the bronchitic postmen surveyed, but the total excess in bronchitic incidence over the control level was only partly explained by the adverse experience of this group These men have also more absences from other causes than the corresponding " controls ", but the excess is only a quarter as great as for bronchitis and asthma, and 20% of these men died either in the service or within the period of follow-up Thus although psychological factors can obscure its pattern, the sickness record in earlier adult life may have some value in identifying men more likely to develop disabling respiratory disease

Berkson (1946) has pointed out the fallacy inherent in the use of hospital admission records to identify significant associations of two or more diseases reported in the same individual Quite apart from any medical considerations about the severity of complicated disease, an individual with two serious conditions is statistically more likely to be admitted to hospital than a patient with only one To some extent the same argument applies to premature retirement on health grounds, but comparison of the frequency of diseases other than bronchitis among the " controls " drawn at random from the same population should minimise the risk of overestimating the significance of any associations found In the circumstances, the finding of an excessive incidence compared with the standard rate of peptic ulcer and of death from cancer of the lung and coronary disease does suggest that smoking may be a factor common to the development of conditions which have all been shown to be associated with cigarette consumption (Doll and Hill 1956, Hammond and Horn 1957) Browne and Vineberg (1932) pointed out that hyperchlorhydria may result from the high arterial carbon-dioxide level in emphysema, but the abnormal coincidence of peptic ulcer and chronic bronchitis is as likely to be due to the aggravation of both diseases by smoking Because of the real possibility of diagnostic confusion between the later stages of disease of the respiratory and circulatory systems, however, this evidence can be regarded as indicative rather than absolute Again, since no smoking histories of either " bronchitics " or controls could be obtained, the role of smoking as a contributory cause of regional and other differences in the natural history of bronchitis cannot be assessed

Summary and Conclusions

In this study of the evolution of chronic bronchitis disease in a homogeneous occupational group widely dispersed over the country, the sickness-absence records for the whole of their service of postmen who were permanently disabled by chronic bronchitis, or who died from this cause, while still in the service are compared with those of other postmen of the same age still actively employed in the same area and with comparable length of service The incidence of all forms of respiratory disease at all ages from 20 to 59 is contrasted in the two groups

The pattern of disease, including the incidence of serious pneumonia, pleurisy, and circulatory disturbances, was also compared in groups of bronchitic postmen who had worked in four divisions of the country graded according to presumptive air pollution based on fog frequency The time-relations of onset of attack of bronchitis and contemporary fog and climate were studied in the histories of bronchitic postmen working in the London area

Those men who were given pensions on retirement on health grounds were followed until death or up to seven years after the date of invaliding Their mortality experience by cause was then compared with expectations based on national age-sex specific death rates Comparisons were also made between survival rates in the more and less heavily polluted parts of the country

From the analysis of these data, several significant findings emerged

(1) Postmen who were ultimately disabled or who died prematurely from chronic bronchitis had more and longer absences than their controls even in early adult life This excess was partly due to the presence among them of a minority prone to absence because of asthma and from all causes, including respiratory disease

(2) After the age of 45 the "bronchitics" became rapidly worse with 8–10 times as many attacks of pneumonia, pleurisy, and asthma as their "controls" Circulatory disorders were particularly excessive among bronchitics who died either while still in the service or within seven years after invaliding

(3) Bronchitic invalids had more disability from peptic ulcer and more deaths from coronary disease and lung cancer than the population at large

(4) Bronchitic postmen who had worked in the more fog-ridden parts of the United Kingdom had, after the age of 45, far more frequent absences from bronchitis, pleurisy, and pneumonia and circulatory disorders than bronchitic postmen from less polluted areas The onset of bronchitic attacks was more closely related to fog frequency than to cold or humidity, and there were clear gradients between the less and more polluted areas in the short-term and long-term prognosis of the disease

These findings lead to the conclusion that there are important differences, probably due to variations in local air-pollution levels, in the character as well as in the frequency of bronchitic disease in different parts of the country Although the coincidence in bronchitics of diseases such as peptic ulcer, coronary disease, and cancer of the lung is consistent with a common origin in smoking, no data on smoking habits were available to confirm or deny its role in the natural history of chronic bronchitis

We are most grateful to Dr W E Chiesman, and Dr M C W Long and their colleagues of the Treasury Medical Service for their help, and to the Post Office authorities for providing copies of the sickness-absence records, for tracing the invalided postmen, and for permission to use the data Both the Post Office authorities and the Registrar General gave much help in ascertaining the cause of death in the follow-up study Miss Linda Colwell did the computing and Mrs Sheila King drew the diagrams

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DIETARY TREATMENT OF MYOPIA IN CHILDREN

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Myopic children in general grow more irregularly and mature earlier than their fellows (Gardiner 1954) The rate of visual deterioration coincides, in both time and degree, with spurts of physical growth (Gardiner 1954, 1955)

Increase in myopia is greater and commoner in children who refuse animal protein in their diet than in those whose tastes are more catholic (Gardiner 1956a) A nutritional problem has been exposed, in that myopic children whose eyes are deteriorating eat less food for every pound they increase in weight than do normally sighted children and those myopes whose eyes are not deteriorating The food element most noticeably implicated is animal protein (Gardiner 1956b)

The present investigation, of which this is a preliminary report, was based on the possibility that rectification of the apparent imbalance of growth and nutrition might diminish the deterioration in eyesight which is seen in most myopic children

Material

The eyesight of two groups of schoolchildren was examined and compared Children known to have congenital myopia were excluded

The control group consisted of the myopic children seen during a period of about six months, at an ordinary school clinic

Most of the treated group were children whose parents elected not to have them seen at the school clinic but preferred or were advised to make their own arrangements (These children were originally seen either at hospital or under the scheme provided by the supplementary ophthalmic service) A proportion, however, came from school clinics other than the ones contributing the control group No other selection was made and there were no refusals to attend The two groups appeared comparable in health, in social class, and in the nature of their myopia, though precise data on these points cannot be adduced Known congenital myopes were excluded from both groups The average height and weight in each group is shown in table I there is no consistent bias

The alternative method—of treating a random selection of schoolchildren—was discarded owing to the difficulty of preventing the spread of information between those being treated and those not, either in the waiting-room, or, as would often have been the case, between children in the same family, one of whom was being treated and the other *not* Dummy treatment in this investigation would have been impossible

Refraction was done in all the children *in* both groups at the outset, six months later, and a year later

Method of Treatment

Each child's diet, as taken at home and at school before treatment began, was assessed using standard tables of food composition (McCance and Widdowson 1946) The same dietitian examined all the children A diet was then devised to enable the child to take 10% of his calorie intake as animal protein, the calories being based on the child's natural appetite No attempt was made to alter the calorie intake Free use was made of 'Casilan' (calcium caseinate) as a supplement for children with an obvious antipathy to animal protein

TABLE I—INITIAL HEIGHTS AND WEIGHTS OF CHILDREN, ACCORDING TO DEGREE OF INITIAL MYOPIA IN DIOPTRES (D)

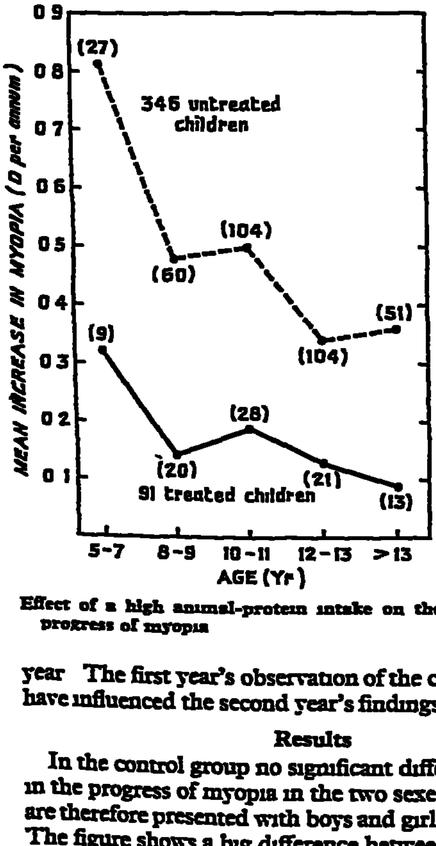
Degree of myopia (D)	Height (in.)		Weight (lb)	
	Control	Treated	Control	Treated
−0·25 to −0 9	55·5	55 3	78 3	76 9
−1·0 to −1·9	55·5	56 4	76 1	78 5
−2·0 or more	55·5	55·9	78·4	79 8

The control group of children was given no dietary advice whatever

Throughout the year's treatment a close watch was kept on deviations from instructions Each child was seen two or three times in the year and the diet adjusted to try to keep the balance at the optimum level

The change in refraction in the treated group during the year was compared with the change in the control group Some of the controls were under observation for two years It was thought justifiable to use these two annual rates of change in the control group as separate observations

In the treated group, it was thought unjustifiable to include the second year's changes in those few whose treatment lasted two years, since the first year's treatment could in theory have influenced the refractive changes in the second year The first year's observation of the controls could not have influenced the second year's findings on refraction.



Effect of a high animal-protein intake on the progress of myopia

Results

In the control group no significant difference was found in the progress of myopia in the two sexes, and the figures are therefore presented with boys and girls added together The figure shows a big difference between the treated and untreated groups, at all ages, in the rate at which the myopia deteriorated In the younger children the deterioration was greater in the controls by 0 5 dioptre (D) per annum (mean figure) In the older children the process was all but arrested in the treated group Table II shows how the eyes of the treated group fared compared with the controls The ratio C/T (control/treated) shows that the more severe the myopia at the start of treatment, the bigger the difference between the treated and untreated groups But this difference bore no consistent relation to age

TABLE II—AVERAGE ANNUAL INCREASE IN MYOPIA

Myopia at start (D)	−0 25 to −0·9		−1 to −1·9		−2·0 or more	
—	No of children	Change (D)	No of children	Change (D)	No of children	Change (D)
Controls	139	−0 39	98	−0·51	109	−0·60
Treated	20	−0 17	26	−0·20	45	−0 18
C/T	2 30		2 55		3 33	

Age (yr)	*Ratio C/T*
5–7	2·53
8–9	3 43
10–11	2·63
12–13	2 62
13–	4 11

In table III the figures have been broken down into subgroups according to age and degree of myopia at the beginning of treatment or observation

Tables II and III show that the treated children deteriorated more slowly than the untreated in every group except at the age of 13 or more in those with the least severe myopia

TABLE III—AVERAGE INCREASE IN MYOPIA IN TREATED AND CONTROL PATIENTS ACCORDING TO AGE

Age (yr)	Initial myopia (D)	−0 25 to −0·9		−1·0 to −1 9		−2·0 or more	
	—	No of children	Annual change (D)	No of children	Annual change (D)	No. of children	Annual change (D)
5–7	Control	10	−0·6	8	−0 72	9	−1 12
	Treated	5	−0 32	1	−0·60	3	−0 23
8–9	Control	24	−0·44	18	−0·54	18	−0 53
	Treated	3	−0·0	6	−0·05	11	−0 22
10–11	Control	46	−0·45	26	−0·58	32	−0·51
	Treated	5	−0·22	11	−0 19	12	−0 17
12–13	Control	40	−0·25	36	−0·40	28	−0·40
	Treated	5	−0·04	2	−0·15	14	−0·16
>13	Control	19	−0·23	10	−0·33	22	−0·46
	Treated	2	−0 25	6	−0·02	5	−0 10

The biggest increase in an individual child was 2 3 D in a year in the untreated group and 1 6 D in the treated group In general the treated group deteriorated at about a third the rate of the untreated (see figure)

Table III also reveals that the distribution of myopia differed in the two groups, there were relatively more severe cases in the treated than in the control group Moreover, in the control group, the more severe the myopia at the beginning of the period of observation, the more it progressed. This is an interesting observation on its own account, and is not shown in the treated group

TABLE IV—RELATION OF THE AMOUNT OF ANIMAL PROTEIN CONSUMED IN THE TREATED GROUP TO THE MEAN CHANGE IN MYOPIA (D)

% of calories taken as animal protein	Initial degree of myopia (D)	0·25–1·9		>1·9		Average of means
	Age (yr)	<12	>12	<12	>12	
<8 1		−0 24	−0·23	−0·11	−0·33	−0 23
8 1–8·9		−0 20	−0·22	−0·26	−0·35	−0·26
>8·9		−0 15	−0 20	−0·28	−0·03	−0·06

+ = improvement.

The object of the treatment was to try to give 10% of the calories as animal protein. At the end of the period an assessment was made of the actual proportion taken in this form It proved possible to divide the children into those who took up to 8 0% of their calories as animal protein, those who took 8 0–8 9%, and those who took more than 8 9%

The changes in refraction in these subgroups are shown in table IV

In three of these four subgroups, those who took the most protein deteriorated least, and the average shows

TABLE V—RELATION OF THE AMOUNT OF ANIMAL PROTEIN CONSUMED IN THE TREATED GROUP TO THE MEAN DETERIORATION IN MYOPIA (D)

% of calories taken as animal	Age (yr.)	<12				>12			
	Initial myopia (D)	−0·25 to 1·9		−2·0 or more		−0·25 to −1·9		−2·0 or more	
	—	No of children	Change	No of children	Change	No of children	Change	No of children	Change
<9·0	Boys	7	−0·37	6	−0·17	8	−0·24	3	−0·37
>8·9		8	−0·06	2	−0·40	3	+0·23	4	+0·18
<9·0	Girls	9	−0·08	6	−0·25	4	−0·12	5	−0·32
>8·9		5	−0·28	8	−0·25	1	+0·10	5	−0·17

+ = improvement.

clearly that there is a big difference in the change in myopia between those children with the highest protein intake and the others. Those over 12 years of age have done better than those under 12. But the figures in table IV are not significant statistically—even if those over 12 years of age only are considered (P=0·07).

If the sexes are separated the results shown in table V are obtained.

Excluding the girls under 12 in table V, P=0·02. Therefore it is very unlikely that the differences in the myopic process in this table between those who took the smaller and those who took the larger quantity of protein are due to chance. The figures for the subgroups in table V are not significant. These figures indicate that in five out of eight subgroups the higher intake of protein is associated with a much reduced rate of deterioration of myopia in the treated group of children. In three out of four subgroups of those over 12 the mean degree of myopia improved.

Discussion

The difficulties of controlling a clinical experiment such as this are numerous. Myopia develops in a haphazard way, and though the process is most active amongst younger children, which may possibly mean that it is most active at its inception, new cases are continually arising at all the growing-ages. Since children's eyes are examined relatively infrequently, it is very hard to establish, in a given case, precisely when myopia has begun. In this investigation, so far as is known, the estimate of refractive errors was made, in both groups, at a random moment in the progress of the myopia, and there should therefore be no difference between the two groups in the duration of the disease.

The validity of the results depends largely on the similarity of content of the treated and untreated groups.

Both consisted of children of all ages, but not all the treated children were taken out of the school clinics. Certainly the treated group contained a greater proportion of higher myopes. It is possible that some of their parents were more anxious about the welfare of their children's eyes than those at the school clinic, but I find it hard to believe that this would influence the outcome favourably. These children's eyes would not be likely to be worse than those of other children if their parents *could* by care and trouble improve them—especially if this improvement depended on general healthy environments. The contradiction is obvious.

There was, in my opinion, no discernible difference between the outlook and type of child and parent who happened to be directed to the treated group and the type of child and parent who attended the school clinic (untreated group).

The fact that in the control group progress was proportional to the severity of the myopia (table II) seems to militate against treatment being as successful in children with severe myopia, yet they are the ones that did best (table II) and were more common in the treated group.

It must be admitted that, by strict statistical standards, selection was not random, and therefore there may have been some unknown factor of selection or dissimilarity between the groups which influenced the outcome. This possibility seems remote and no sensible guess can be made about it.

The one consistent difference between the two groups is that the treated group consumed a high quantity of animal protein. If this contributed to the difference in the rate of deterioration between the two groups, it would be reasonable to suppose that those who consumed the most would have done the best. In the treated group this was found to be broadly true, though *under the age of 12 in the girls it could not be established.* None the less, over the rest of the field of inquiry the figures show a strong tendency towards an effect being obtained in the children taking over 9% of their total calories as animal protein.

A clue to the anomalous behaviour of the girls under 12 may be obtained by studying their growth. Their weight increased by 15·1% during the year's treatment, whereas the weight of the boys of the same age increased by only 11·7%. The height increase in the two groups was about the same, and their dietary intake also was similar. Previous studies in untreated children have shown that myopia is likely to increase faster in children with a high weight-height ratio (Gardiner 1954).

Secondly, the animal-protein intake per pound increase in weight is much lower in children with progressing myopia than in those with stationary myopia (Gardiner 1956b). The animal protein intake of these girls during the year's treatment was similar to that of the boys, but they increased in weight substantially faster than the boys.

It is hard to imagine how the group of treated children differed from the untreated in any way which would affect the issue, and even harder to conceive of a common reason for this and for the fact that those who carried out the treatment to its full tended to do best. The most likely reason for my findings is that the high animal protein intake was beneficial.

The supporting evidence is in favour of this probability. I have previously shown that, compared with normally sighted children, myopic children more often refuse animal protein (Gardiner 1956a). Moreover, hypermetropia in a growing animal can be reduced by limiting the protein content of the diet (Gardiner and Macdonald 1957).

As already mentioned, casilan was offered to children whose appetite or taste prevented them from taking their animal protein as ordinary food, and here again there was considerable variation in the children's acceptance of the treatment and in their response. In the 16 children who consumed the amount of casilan advised, the mean change in refraction was an improvement of 0·02 D, in the 42 who took some casilan, the mean change was a deterioration of 0·16 D, and in the 14 who refused to take any casilan the mean change was a deterioration of 0·22 D.

These figures relate to changes in six months, and represent an extension of the work already described. Many of these children were not included in the other results because a year's treatment had not been completed. The trend here is clear, and the deterioration of 0·22 D in six months in the worst group is comparable with that of the worst in the main treated group who deteriorated 0·32 D in a year. The deterioration in the casilan-treated group was in fact rather worse—as one would expect, since they were put on casilan because their protein intake, even on the diet, was too low.

Arising out of the main investigation various subsidiary results have been obtained. These show that milk plays an important part in the control of myopia and that some part is played by the vegetable protein intake These will be the subject of a further communication

All these findings need further elaboration, but they are strongly in favour of a dietary influence on the course of myopia in growing children and adolescents It is certainly possible that the balance of the diet, and not the animal-protein content, may be a factor, since it has been radically changed by the treatment. However, it is impossible to establish this without a rigid control of both carbohydrate and fat intake

The findings throw no light on the pathological processes involved in myopia, and some of the incongruities may be explained if myopia has more than one cause They have no direct bearing on possible causes of myopia, since all the children had established myopia when the investigation began

Until reliable figures for the incidence of myopia can be obtained in different places and at different times, and until a suitable experimental animal can readily be induced to become myopic, research into the causes of myopia will be halting

Discussion of Technique Involved

From the practical point of view it is extremely important to have an accurate assessment of the diet—both of the calories yielded and of its constituents This information can be obtained only by a trained expert It is useless, both for scientific and for clinical purposes, merely to ask general questions about the diet Experience shows that patients cannot answer questions about their food at all accurately unless the questions are asked in great detail, and even then there is room for individual interpretations of the replies given Probably no two dietitians would agree on the constitution of a patient's diet, but I have been fortunate in having the same dietitian through all these investigations Hence in this investigation it is possible to compare results in different patients and in one patient at different times These comparisons would not be so easily made with a team of dietitians and would be impossible without a dietitian at all

Some of the children have shown a tendency to put on weight, some have what seems to amount to an anorexia, some are extremely particular in their tastes, some are energetic, some lazy, most are growing irregularly, some are well to do, and some are "on welfare" All these factors have had to be taken into consideration, and diets and advice have to be adjusted in every case for the individual None the less it has been possible to reach a level of animal-protein intake of 9 0% of the calories in 43% of the children, and these have done better than the rest

Summary and Conclusions

In a group of shortsighted children who attended the research clinic at Guy's Hospital and received extra animal protein, the rate of visual deterioration was much less than in a group who attended the ordinary school ophthalmic clinic and whose diet was not changed

The difference in treatment between the two groups lay primarily in the increased amount of animal protein consumed by the treated group, though it is clear that other factors are at work

With a few exceptions among the younger children, those who carried out the treatment most assiduously tended to deteriorate more slowly than their more casual fellows Of the children over 12, there was actual improvement in most of those who took the greatest quantity of animal protein

Whatever may be the cause of acquired myopia in children and adolescents, its course can be beneficially modified by dietary means The factors involved still need elucidation

This work has been done partly with facilities from the Endowment Fund of Guy's Hospital, and in particular I am grateful to Mr Frank Law for his support I could not have produced the results without the cooperation of Dr K M Bodkin, area medical officer of health for Hendon (Middlesex County Council) and her staff of health organisers The dietetic work has been shouldered entirely by Mrs V Zivanovic, and my indebtedness to her is great Lastly I must mention the intensive secretarial work done by Mrs A. D Holland

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EPIDEMIOLOGY OF ARTERIOSCLEROSIS IN ISRAEL

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THE study of geographical variations in pathology and of world-wide epidemiology are expected to give the answers to questions of ætiology where the purely clinical approach has so far failed Malignant neoplasms are being thus investigated, but in other diseases which possibly result from long-term environmental effects there is need to supplement clinical by global epidemiological research Foremost among these—with regard both to the urgency of the problem and to the variety of approaches used—is arteriosclerosis

In Israel the "ingathering of the exiles" has produced a population of the most varied geographical extraction, physical habitus, and cultural background, which can still be studied in distinctive groups

Here the computation of age-specific mortality-rates for groups of different geographical origin revealed unexpected differences in the localisation of arteriosclerosis

This study is based on deaths assigned to arteriosclerosis according to the Manual of International Classification of Diseases, Injuries and Causes of Death (World Health Organisation, 1948) Cerebral arteriosclerosis refers to nos 330 to 334, coronary-artery disease to nos 420,0 and 420/1 of this classification

It was found that, within each age-group, coronary and cerebral arteriosclerosis show different patterns of distribution with regard to the sexes, the geographical origin, and the time since immigration

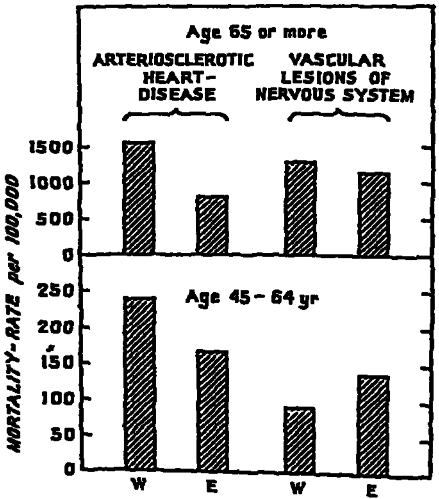

Fig 1.—Mortality-rates (per 100,000) in two disease- and age-groups, by continent of birth (1953-54) E, oriental, W, occidental.

MORTALITY-RATES (PER 100,000) BY TWO DISEASE- AND AGE-GROUPS

Factor	Group	Arteriosclerotic heart-disease						Vascular lesions of central nervous system					
		Age 65 or more			Age 45–64			Age 65 or more			Age 45–64		
		Rate	Difference	Significance of difference*	Rate	Difference	Significance of difference*	Rate	Difference	Significance of difference*	Rate	Difference	Significance of difference*
Continent of birth (average 1953–54)	*Occidentals*	1532±41	790±72	+	232±8	72±15	+	1237±37	106±69	–	86±5	49±10	+
	Orientals	744±46			161±12			1133±57			135±11		
Sex and continent of birth (1954)	*Occidentals* Males	2040±100	1024±114	+	355±19	256±22	+	1199±77	2±103	–	91±9	11±13	–
	Females	1015±62			99±10			1197±68			80±9		
	Orientals Males	638±84	103±113	–	216±26	104±33	+	847±95	114±140	–	97±18	38±27	–
	Females	535±76			122±19			961±102			134±21		
	All males	1627±73	737±67	+	308±15	211±18	+	1127±61	14±83	–	90±8	10±12	–
	All females	890±48			98±9			1142±56			100±9		
Continent of birth and time since immigration (average 1953–54)	*Occidentals* Newcomers	1399±65	149±79	–	200±11	12±15	–	1097±58	72±70	–	93±8	27+9	+
	Veteran settlers	1250±46			212±10			1024±42			66±5		
	Orientals Newcomers	544±50	47±82	–	141±12	3±26	–	930±65	255±101	+	132±12	38±43	–
	Veteran settlers	591±67			138±21			674±71			94±17		
	All newcomers	1235±49	110±61	–	178±8	24±12	–	1028±43	170±61	–	107±7	38±9	+
	All veteran settlers	1125±40			203±9			960±37			69±5		

* Criterion of significance 2×standard error

From the table and figs 1–3 it appears, as the most characteristic and most unexpected feature, that for arteriosclerotic heart-disease, in both the age-groups studied, there is a distinct preponderance of people of occidental over those of oriental origin,* but this preponderance is absent or even reversed in direction for vascular lesions of the nervous system (fig 1)

Similarly there is an excess of males over females in all the age and ethnic groups for the coronary localisation, but not for the cerebral one (fig 2)

Moreover, the rates are more or less similar in newcomers to the country and in veteran settlers, for coronary arteriosclerosis in the two age-groups studied in orientals and occidentals alike, whereas there is an excess of newcomers in the corresponding deaths from cerebral arteriosclerosis (fig 3)

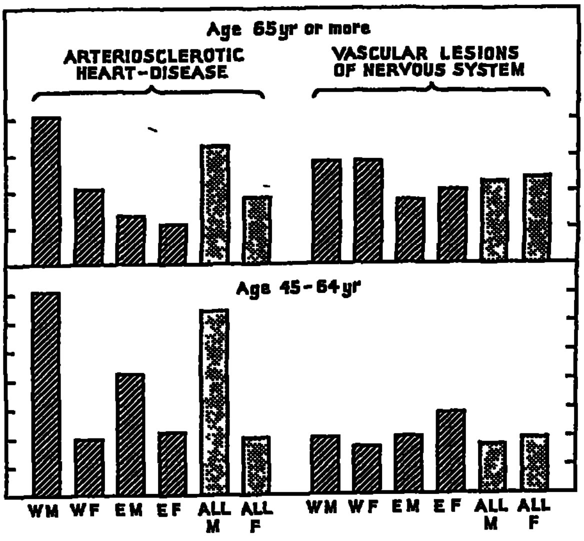

Fig 2—Mortality-rates (per 100,000) in two disease- and age-groups, by sex and continent of birth E, oriental, W, occidental, M, male, F, female

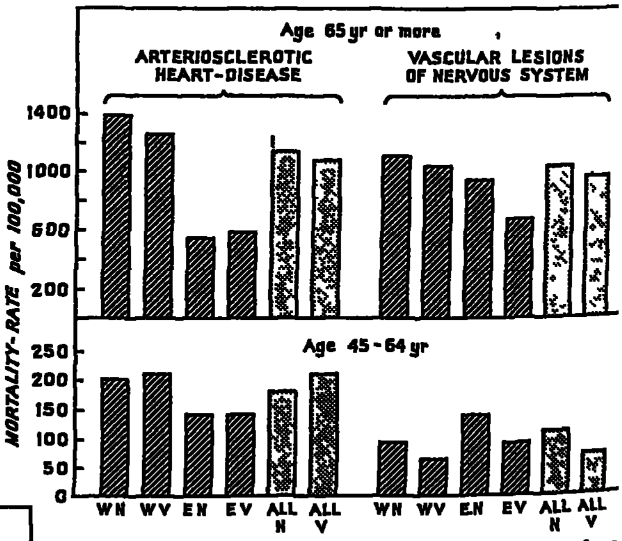

Fig 3—Mortality-rates (per 100,000) in two disease- and age-groups, by continent of birth and time since immigration E, oriental, W, occidental, N, newcomers (after 1948), V, veteran settlers (before 1948)

If any conclusion may be drawn from these data it must be tentative It seems that coronary and cerebral arteriosclerosis, following as they do different epidemiological patterns, may be two basically different phenomena It has also been suggested that we may be dealing with different intensities of one and the same pathological process

Thanks are due to Prof F Dreyfus, deputy director of the medical department A of the University Hospital, *Jerusalem*, and to Dr F Yekutiel, director of the epidemiological department of the Ministry of Health, for their kind assistance and constructive criticism

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* The terms "orientals" and "occidentals" are used here to signify the broad groups of Jewish immigrants to Israel with country of birth on the Asio-African and European continents respectively The second group coincides roughly with the accepted term of "Ashkenasian" Jews

AN UNUSUAL CASE OF CARDIAC INJURY

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CARDIAC injuries of every conceivable type have been described over the years No claim is made for the uniqueness of this case, its interest lying chiefly in the mode of causation

Case-report

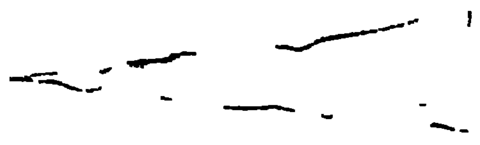
A man, aged 32, of good physical stature, was admitted to hospital at 1 30 P M on Aug 5, 1957, in a collapsed state At about 11 45 A M that day he had been in a greenhouse helping his brother, who was replacing some glass tiles The height of the roof was 14 ft While the patient was standing directly below, his brother accidentally broke a pane with his elbow, sustaining no injury himself The patient immediately cried out that he was hurt, and collapsed

On examination he was gravely shocked, pulse and blood-pressure being unrecordable, respirations gasping, and mucosæ pale and cyanosed There was no distension of neck veins A small skin wound about 2 cm long was noted in the right third intercostal space close to the sternal border Blood was welling out of this wound, and the clothing was heavily bloodstained Radiography during resuscitation showed a large right-sided effusion and displacement of the mediastinum to the left Aspiration produced 4 pints of blood After the rapid infusion of 5 pints of plasma the patient's condition somewhat improved, his systolic blood-pressure now being 70 mm Hg As soon as blood was available for transfusion, he was taken to the operating-theatre

Anæsthesia was induced and maintained with 50% nitrous oxide and oxygen, a cuffed endotracheal tube having been passed under topical analgesia Respiration, after having been assisted, readily became controlled on a closed circuit, without any need for relaxants Intravenous infusions were continued into both external jugular veins, no other veins being accessible

Operation —Right thoracotomy was done in the supine position with a slight lateral tilt and a head-down tilt of 20° The incision was in the third intercostal space The right internal mammary artery and the right phrenic nerve were found severed, and the pleural cavity full of blood There was a laceration in the pericardium and in the right auricular appendix A triangular piece of glass 6 5 cm long, 1 8 cm wide at the base, and pointed at the apex, shaped like a scalpel blade, was found embedded in the right auricular appendix The middle lobe in the path of the splinter was lacerated at several places The auricular appendix, from which blood was gushing, was clamped, the internal mammary artery was ligated, and the lacerations of the lung and right auricular appendix were repaired, complete hæmostasis being achieved The wound was excised, and the incision was closed in layers, with underwater drainage

Postoperative course —At the end of the operation the patient's condition was satisfactory, his blood-pressure being 90/60 mm Hg 10 pints of blood had been given by then The transfusion was continued, and oxygen was administered with Boyle's apparatus The patient was breathing adequately and was now conscious For two hours his condition remained unchanged, then his blood-pressure began to fall No response was obtained to noradrenaline, but intravenous hydrocortisone brought about a temporary improvement The systolic blood-pressure, however, did not rise above 80 mm Hg At 12 45 A M the patient collapsed and, despite cardiac massage, died About 3 pints of blood was in the drainage bottle In the postoperative period 5 bottles of blood and 3 of plasma were given, bringing the total to 15 and 8 respectively At necropsy Dr W M F Hall confirmed the operative findings and the satisfactory repair of the damage, and found 2 pints of blood in the right hemithorax



Glass splinter (actual size)

Comment

Massive hæmorrhage into the pleural cavity and externally usually causes immediate death by exsanguination, and injuries causing such hæmorrhage in civilian life are rarely seen in medical practice (Chamberlain et al 1956) In the present case the cause of death was probably prolonged hypotension before treatment, this produced irreversible shock, which only responded temporarily to attempts to raise the blood-pressure

It is unusual for so small and so light a body (see figure) to cause a fatal and so extensive an injury The initial velocity of the fragment could not have been great The splinter fell about 10 ft, probably it was a bigger piece and acquired sufficient velocity to pierce a shirt, a vest, and an undoubtedly muscular chest wall Also its fall was vertical, and a superficial, and perhaps larger, portion of this splinter broke off at the level of the body wall, leaving the main offender inside to do the fatal damage

Our thanks are due to Mr J S A Linton, under whom the patient was admitted, and to Mr A C G Rothera, H M Coroner for the city of Nottingham, for permission to publish

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Preliminary Communication

APPARENT INCREASE IN BLOOD-PROTHROMBIN DURING EXTRACORPOREAL BYPASS AND DURING SLOW COAGULATION IN SILICONED CONTAINERS

POSTOPERATIVE bleeding is becoming more common because of the more extensive operations now attempted It is a very serious complication when it takes place after an extracorporeal bypass for open cardiac surgery

During research into this problem fibrinogen (measured by spinning out the fibrin on a weighed glass rod and then drying and reweighing the rod), platelets (measured by the method of Brecher and Cronkite [1]), antihæmophilic globulin (measured by the method of Pitney [2] as modified by Mustard [3]), and prothrombin (measured by the two-stage method of Biggs and Macfarlane [4] and the acid-precipitated-globulin method of Douglas [5] as modified from the original method [6]), were studied in an effort to ascertain what was happening in the extracorporeal

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circuit It was found that, during thirty minutes on the extracorporeal circuit in the dog, the fibrinogen decreased to 53–63% of normal,[7] the platelets decreased to 55–70% of normal,[7] the antihæmophilic globulin decreased to 40–64% of normal,[3] and the prothrombin apparently increased during the first twenty minutes on the circuit and then decreased in parallel with the other factors

This apparent increase in the amount of prothrombin was first discovered with the two-stage prothrombin-area technique, but since there was such a high single peak in the first minute, it was felt that this increase was due to the inaccuracy which would occur in the area under that peak As a result of this, the acid-precipitated-globulin method was used, and this confirmed the previous results The blood in the extracorporeal system was inhibited from clotting by the use of heparin (Connaught) 4 I U per ml of blood The samples of blood were taken directly from the pump in siliconed needles and syringes during the operation

It is felt that these results indicated that the blood was clotting slowly in the extracorporeal circuit In an effort to confirm this, blood was taken into a siliconed beaker, where it was allowed to clot slowly Samples were taken from this and placed in siliconed test-tubes containing heparin (Connaught) 4 I U per ml of blood The acid-precipitated-globulin method of determining prothrombin was applied to samples taken every minute during the time that the blood was fluid This method gave results which follow exactly the previous findings, showing that, during the clotting of the blood, the thrombin yield of the acid-precipitated globulin increased to an amount greater than twice the initial value This was accomplished within the first two minutes with the siliconed-flask technique and within the first twenty minutes on the extracorporeal circuit These findings were confirmed again by the two-stage prothrombin technique

The extracorporeal circulation system and the siliconed-vessel techniques provide an excellent means of studying delayed coagulation of blood In using Douglas' acid-precipitated-globulin method and the two-stage prothrombin-area method we are measuring the amount of thrombin generated in the samples It is not yet clear that this is due to the activation of a "prothrombin precursor," as suggested by Bordet[8] and Quick and Stefanini[9] or to the activation of a prothrombin "converter" which in turn increases the yield of thrombin from the prothrombin, thus confirming the work of Ware and Seegers[10]

We wish to thank Dr S H Jackson for his valuable assistance and for the use of his laboratory, and the Ontario Heart Foundation for supplying funds to one of us (W T M) for this research

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New Inventions

APPARATUS FOR REMOTE INJECTION IN RADIODIAGNOSTIC PROCEDURES

IT is now commonplace for radio-opaque media to be injected into patients during radiography, and often the same operators are exposed repeatedly to X rays Those who undertake this form of injection are wise to protect themselves from undue irradiation by using some means of doing this from a distance[1] We describe apparatus designed for this purpose

If safety is to be obtained by distance, the needle must be connected to the syringe by a considerable length of tubing If this tubing is thick and heavy it drags on the needle and displaces it The ideal tubing should be light, transparent, and capable of resisting any pressure the syringe can deliver, moreover it should withstand repeated sterilisation by heat, including the autoclave, and no special skill should be required when its replacement is necessary Nylon tubing of a bore slightly greater than the needle fulfils these requirements admirably (no 4 gauge—*Portland Plastics*) *Special connectors* are used to join needle and syringe to this tubing without any reduction in the effective lumen, flanging of the tube ends is not necessary

The nylon tubing passes through the connector and its rubber diaphragm (fig 1), when the screw collar is firmly tightened the rubber is compressed and grips the tubing Although it is possible forcibly to drag the tubing out, this requires far rougher usage than is likely in practice, certainly the maximum hydraulic pressure likely to arise within the tube system is unable to push it out As the connectors have Luer lock ends, the whole system is extremely secure The connector nearest the syringe incorporates a tap to prevent either emptying by siphonage or unwanted entry of arterial blood Thus, the basis in any set for radiodiagnostic injection procedures is an all-glass Luer-lock syringe and nylon tubing with connectors, the nylon tubing may be as long as suits the safety requirements of the operator During sterilisation the tubing must be

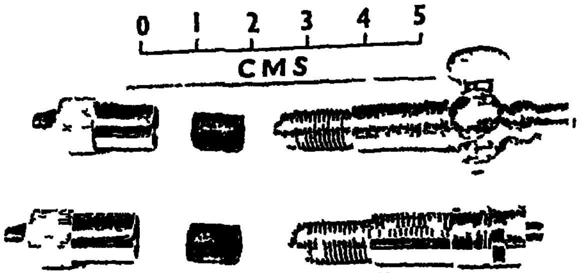

Fig 1—Component parts of a pair of nylon tubing connectors

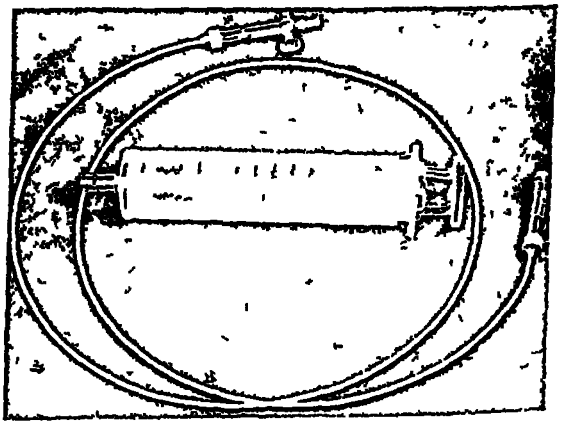

Fig 2—Basic set for radiodiagnostic injection procedures

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[1] Code of Practice for the Protection of Persons Exposed to Ionising Radiations H M Stationery Office 1957

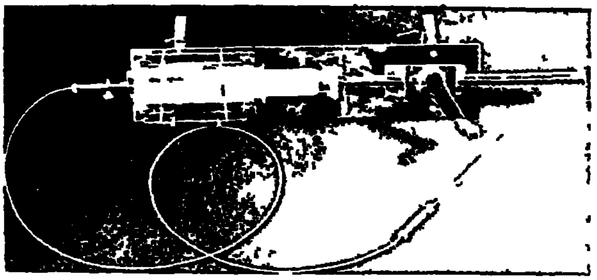

Fig 3—Syringe-pushing device

removed from the connectors because otherwise, softened by the heat, it collapses within them

The provision of a basic set (fig 2) common to a number of techniques, and requiring only simple additions for certain variants, has been found to simplify the task of the nurses in preparing these sets, moreover, the design has reduced maintenance difficulties to a minimum The only parts in the basic set which need occasional replacement are the nylon tubing and the rubber diaphragms in the connectors—the former is simply cut from a roll of 'Portex' no 4 nylon tubing, and the latter are laid into the screw caps after removal of the old diaphragms

Though the syringe may be held in the hand, we have found that for the abdominal aortogram it is much more convenient to use a mechanical device (fig 3) This is not to say, however that we condone delivery of the dye with great force. We believe that high pressure is neither necessary nor desirable and that dissection of the aortic wall [2] may be avoided by use of apparatus which works at low pressure and imparts an instant sense of resistance if the needle is not properly situated Our apparatus has been designed to give a slight mechanical advantage and to retain a sensitivity that is lost if the syringe is pressed home strongly Injection is conducted effortlessly with one hand almost at arm's length, with no tendency to drag on the tubing and no fear of the syringe breaking in one's hand

Fig 3 shows our device, which in its essentials is a "window winder" mounted on a platform so that rotation of the handle extends the thrust arm against the syringe piston, attached to the platform are screw clamps for fixing it to an X-ray table or any other convenient support The syringe (50 ml Luer lock/Summit) is retained in its supporting channel by two spring-clips and is prevented from sliding by a vertical end-piece The thrust arm meets a stop just before the syringe closes completely and avoids this usual source of syringe breakage We do not use an automatic switch coupled to the X-ray machine, but this could be included without difficulty

In our experience, during X-ray exposures the operator is about three feet from the patient, and when one abdominal film and two films of the patient's lower limbs are taken the total radiation received by the operator is less than a milliröntgen This dosage is reduced to a thirtieth by wearing a lead rubber apron, as we always do The radiation dose is then about 1/9000 of the maximum permissible weekly dose of 300 milliröntgens [3]

The same apparatus, including the "syringe pusher", is used in this hospital for splenoportal venography and has been found entirely satisfactory The same basic set, with the addition of appropriate needles and cannulæ, has been used repeatedly for femoral arteriography, peroperative cholangiography, and presacral retroperitoneal insufflation of oxygen For these procedures the syringe is, of course, operated by hand

For oxygen insufflation, a necessary addition to the set is a Luer-lock two-way tap, the side arm of which is connected to a bag of oxygen. The original technique used a syringe, two-way tap, and needle locked together [4], the insertion of nylon tubing is an improvement as it enables the operator to sit comfortably alongside the patient The nylon tubing, resistant as it is to collapse by suction, allows instant detection of any blood drawn back into its lumen

We are indebted to Dr F T Farmer for the data on radiation dosage

We acknowledge the valuable assistance of Messrs Robert Whitelaw (Newcastle) Ltd, 44, Great North Road, Newcastle upon Tyne, 2, in the development of the connectors, this firm has undertaken to supply all the equipment referred to The nylon tubing may also be obtained from its makers—Messrs Portland Plastics, Bassett House, Hythe, Kent.

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Reviews of Books

Sherrington Physiologist, Philosopher, and Poet

LORD COHEN OF BIRKENHEAD, M.D, D SC, LL D, F R C.P, professor of medicine, University of Liverpool Liverpool University Press 1958 Pp 108 17s 6d

IN 1948, on the occasion of the ninetieth birthday of Sir Charles Sherrington, the council of the University of Liverpool instituted a biennial lectureship in his honour, and to commemorate his association with that university, as professor of physiology, for eighteen years This volume contains the three addresses in this series which were delivered by the professor of medicine, Lord Cohen of Birkenhead

The last word about Sherrington's contributions to physiology will not be written for many years to come His *Integrative Action of the Nervous System* has been knowledgeably compared with such scientific milestones as Harvey's *De Motu Cordis* and Newton's *Principia* Lord Cohen's lectures give an admirable and fascinating outline of this talented and varied life Two episodes alone need be mentioned to illustrate the versatility and enterprise of Sherrington there are good grounds for believing that he was the first doctor in this country to use the antitoxin, which Behring had discovered, to save a patient dying of diphtheria, and when, during the 1914–18 war, he was asked to study fatigue in munition workers, he tackled the problem by working in a shell factory, as an ordinary labourer, twelve hours a day, for three months

All who knew Sherrington, and all who read in this book of his contributions to science and literature, will feel that Lord Cohen chose aptly when he applied to him an epitaph once used by Samuel Johnson of another doctor, philosopher, and poet *Nullum quod tetigit non ornavit*

Tuberculosis in Animals and Man

A Study in Comparative Pathology JOHN FRANCIS, D SC., M.R C.V.S, professor of veterinary preventive medicine, and dean, faculty of veterinary science, University of Queensland London Cassell 1958 Pp 357 105s

IN this book Professor Francis has gathered much information of importance to veterinary surgeons and of great interest to doctors The first part is about bovine tuberculosis, and its prevalence in cattle in different countries and in different breeds is described in detail The section on pathogenesis and pathology emphasises how thoroughly the early investigators (including the British Royal Commission on Tuberculosis, which is much quoted) studied the disease in calves, and the account of immunisation includes a comparison of the effects of B C.G and the vole-bacillus vaccine in man Explanations follow of the difficulties of detecting tuberculosis in cattle and of the methods used in different countries for suppressing the disease as completely as possible over a period of years The chapter on bovine-type infection in man is largely a study of the relationship between the types of tubercle bacilli and of the possibility of interchange between the human and bovine types, and the evidence is assembled for the view that, where there is heavy exposure to human droplet infection, ingestion of tuberculous milk enhances resistance to pulmonary tuberculosis in the general population

Thereafter, considerable space is devoted to tuberculosis in all other animals about which there is reliable information, from monkeys to edible frogs, taking in, among others, elephants, camels, and mice A description of avian tuberculosis in domestic and wild fowls is included, and the incidence of avian-type infection is often mentioned throughout this part of the book because of its frequency in sheep and pigs, especially in Denmark and the United States, where bovine tuberculosis has been almost eradicated

A final short section compares the pathology and epidemiology of tuberculosis in animals and man Professor Francis classifies animals according to the general pathological picture, and he finds that those animals in which more or less typical tubercles are formed develop a fairly high degree of allergy Primitive man faced with civilisation, and monkeys taken into captivity, are very liable to fatal infection a primary complex develops and their histological reactions are similar Experimental infections in guineapigs and rabbits show the same reactions Urban man and all bovidæ come into the next group, which shows moderate susceptibility to infection and reacts with typical tubercles Horses are much more resistant to infection and their lesions consist of chronic granulation tissue without typical tubercles In most other animals there is no tubercle formation, though some may show necrosis and liquefaction, and many are very resistant to infection Professor Francis also discusses the ideal experimental animal, the virulence of tubercle bacilli for various species, and natural infections in such species An appendix gives brief summaries and a complete list of the reports of the Royal Commission on Tuberculosis

Professor Francis has ranged very widely and brought together much scattered material which he has skilfully woven into a very valuable book Some readers may regret that he has not expressed more definite views on some of the controversial issues that abound in this subject, but the difficulties of doing so are very apparent All who are involved or interested in the eradication of tuberculosis, especially from the animal world, will be grateful for the help and stimulus of this book

Liver-Brain Relationships

IAN A BROWN, M D , PH D , associate professor of neurology, University of Minnesota Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1957 Pp 198 50s

THE new and expanding views on liver-brain relationships have been elaborated from a thesis to a book by Dr Brown A remarkably international bibliography and a comprehensive historical introduction have survived the transformation best Apart from a chapter on Wilson's disease, the book is devoted to the neuropsychiatric syndrome of hepatic coma British readers will be pleased by the acceptance of factors other than liver failure as causes of hepatic coma, despite the complex nomenclature of the various "hepatoencephalomyelopathies" that this entails The importance of alterations in personality which may precede coma is emphasised, very justly, to a greater degree than is usual

Dr Brown writes at length on his personal experience in 42 cases, a series which is not large or representative enough for this complex subject, and which directs too much attention to routine tests of liver function, neglecting more relevant investigations (such as portal venography or blood-ammonia studies) The electroencephalographic data are somewhat scanty, and neuropathologists may be surprised at the stress laid on demyelination rather than the Alzheimer-cell phenomenon as typical of hepatic coma The possible metabolic basis of hepatic coma is reviewed extensively, though at times uncritically

The book illustrates vividly the neuropsychiatric aspects of hepatic disease—a particularly important consideration in the United States, where liver disease is the third commonest cause of death In this country, those interested in neurology, psychiatry, and gastroenterology will find it valuable, and it can be commended to a wider public as a good example of the complexities of this kind of research

Sentenced Without Cause

DAVID ROXAN London Frederick Muller 1958 Pp 255 18s

Too few people realise that, despite the absurd complexities of existing legislation, detention in one of our less pleasant mental-deficiency institutions may be brought about in a very perfunctory way It is easy to describe a person of uncertain I Q as "feeble-minded" or another with some character eccentricity as a "psychopath" To lock up such people under an unenlightened regime is likely to produce behaviour abnormalities which may then be held to justify further detention What is called "treatment" may be a system of graded incentives to good behaviour in a prison-like atmosphere working up from an extreme of degradation

Some inadequacies of the present system are vividly described in this book, which recounts the life of an orphan who trod the gloomy trail from one bad institution to another via casual intelligence tests and brief psychiatric interviews, ending (illegally and undeservedly) at Rampton Doubtless there is much special pleading here questions are begged and the writing is emotionally biased, one wonders whether the subject of the work has shown himself, since discharge, to be as normal as the book makes out (though after his sad life it would be remarkable if he were) In all, however, the picture is probably true, and it may help to produce that climate of opinion that seems necessary before reforms can be achieved Until more money is provided for this branch of the health service, these deficiencies cannot be eradicated

The author asks whether this is an isolated instance or whether, among the 30,000 detained in such institutions, there are many well able to take their place in society This question is impossible to answer under circumstances where even psychiatrists are sometimes refused access, but there is reason to suppose that the situation is by no means satisfactory

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Mental Disorder (National Association for Mental Health, London 1958 Pp 35 3s)—The report of the Royal Commission on the Law Relating to Mental Illness and Mental Deficiency is surveyed in this handy booklet by Mr C H Rolph He threads a devious but always intelligible course through the tangle of existing laws and opinions, he gives a few views of his own and makes the whole affair clear and of interest to the layman Obviously there is a wide public for such a work, particularly among those working on the fringes of the welfare services, who find the report itself (with some 300 crowded pages) a formidable undertaking He may be too uncritical of the section on psychopaths, perhaps the weakest part of the report, but he has done his best to take in the contrary views that have been expressed since it was published a year ago he is certainly right up to date Reviews, criticisms, evaluations, and opinions on the Royal Commission's findings are thick on the ground, but this is a pamphlet well worth having

5-Hydroxytryptamine (London and New York Pergamon Press 1958 Pp 253 60s)—These proceedings of a symposium held in London last year form a useful summary of the information available about an interesting and still mysterious substance Since last year observations on the action of 5-H T relative to intestinal movements may have lightened the mystery, but it is far from clear why 5-H T should be so widely distributed a cell component, or why it should be relatively concentrated in certain parts of the central nervous system The symposium dealt with the occurrence and distribution of 5-H T , its storage and release, and its actions on the cardiovascular system, on nerve-endings and ganglia, and on gastric secretion Its significance in carcinoids was discussed, and its role in anaphylaxis Its central actions were considered as well as its central and peripheral antagonists Thus, the symposium covered much ground and this report, edited by Dr G P Lewis, is a valuable book of reference

THE LANCET
LONDON 31 MAY 1958

The Tourniquet

THE tourniquet is associated in many minds with the era of blood-letting, leeches, and cutting for stone, but even today a Samways tourniquet dangles as a sinister threat from the foot of many an amputee's bed. It is a device which has rendered useful service to surgeons, and it remains a favoured if occasional aid. The original tourniquets of **MOREL**[1] (1674) and **JAMES YOUNG**[1] (1678) were rude contrivances "a wadd of hard linen cloth, or the like, inside the thigh, a little below the inguen, then, passing a towel round the member, knit the ends of it together, and with a balloon or bedstaff, twist it till it compress the wound". **PARÉ**[2] (1561) recommended "a strong broad fillet like that which women usually bind up their haire", and the mechanistic 19th century developed formidable metal gadgets with screw compression. **ESMARCH**'s original elastic band consisted of a rubber tube as thick as a finger. it was **VON LANGENBECK** who suggested the modern type of flat elastic bandage which gives more diffuse pressure. Finally the pneumatic cuff was modified to provide ischæmic compression. this is the most satisfactory type since the pressure can be accurately adjusted and maintained, but it may leak, and it is cumbersome and is not quickly applied. When the cuff is applied to the arm a pressure of 250 mm Hg is usually sufficient, in the legs 300 mm.

The tourniquet is used to staunch traumatic hæmorrhage or to ease dissection in elective surgery. In the control of severe traumatic bleeding a tourniquet has a very limited place. Most types of hæmorrhage are readily and more safely controlled by elevating the limb and by local digital or pad pressure. Only when such measures fail should a compressive band be considered. An inefficient Spanish windlass (a popular type for first-aid kits) may through venous congestion increase blood-loss, or through excessive pressure, especially in the upper arm or below the knee-joint, it may cause nerve damage and by long periods of limb ischæmia lead on release to "tourniquet" shock, gangrene, or precipitous hypotension. Most wartime surgeons felt that more lives were lost than were saved by tourniquets. As an emergency measure soft rubber tubing ($^1/_2$ inch) was generally recognised as simple and effective, although this method was never officially approved. A length of about six feet was applied with moderate tension over a towel, taking four turns around the limb. One particular indication was the high-pressure hæmatoma following injury to a vessel. wartime experience showed that more damage was done by pressure and infiltration from the hæmatoma than by application of a tourniquet for a reasonably short time.

The place of the tourniquet in elective surgery is more debatable. Many, if not all, orthopædic surgeons like to undertake nerve repairs, hand surgery, meniscectomies, and other selected operations where possible in a bloodless field. (But in some other operations—notably repair of fractured olecranon or patella—it is a nuisance rather than an aid.) **PANNETT**[3] expresses disquiet at what he considers the overuse of the tourniquet. What in fact are the dangers? First, pressure damage—radial or median nerve palsy in the arm being commoner than lateral-popliteal-nerve palsy in the leg. But such palsies are extremely rare if a pneumatic cuff is used in the upper limb and if compression by an Esmarch bandage in the lower limb is restricted to the thigh, even for foot operations, in each case the limb being protected by a towel. Tourniquets placed about the forearm and lower leg are often ineffective, since bleeding from incompressible interosseous vessels is likely to continue. In the occasional case where nerve lesions develop, spontaneous recovery of function is the rule[4], but **MOLDAVER**[5] reported seven cases with complete and permanent nerve lesions, in three compression had been applied by a rubber tube, in two by an Esmarch bandage, and in two by an inflatable cuff. All the palsies were in the upper limb, where the nerves are more liable to be squeezed against bone.

The most important thing about putting on a tourniquet is to take it off. This involves a clearly understood theatre routine. a tourniquet-book with times of application and release, and a tourniquet fixed to the table, the direct responsibility of one member (e g, the surgeon or anæsthetist), are well-tried methods. The period of safe compression for any individual patient is largely unknown. It varies with age, environmental and body temperature, and the type of limb damage. **WOLFF** and **ADKINS**[6] suggested that in exceptional cases up to 6 hours was safe, they observed no case of gangrene, nerve damage, or thrombosis in a thousand battle casualties (albeit in healthy young men) in which a tourniquet was left untouched for up to 4 hours. In elective surgery a safe rule would seem to be to release tourniquets within the hour, and only very exceptionally should the limit be extended to 2 hours. **PANNETT** holds that infection is more likely to ensue in a limb dissection performed in an ischæmic field where "the power of immune response is in abeyance"[3]. There is no clear evidence on this point, but there was an impression among some battle surgeons that anaerobic infection was commoner where a tourniquet had been applied. In the other scale is evidence that application of a tourniquet before manipulating fractures diminishes the risk of fat embolism. The postoperative oedema and pain that are said to follow removal of a tourniquet are often due to overtight bandaging.

What place, then, has the tourniquet, and, in brief, what precautions are necessary? It may be used when it makes an operation decidedly easier, and therefore quicker and safer for the patient. Clear-cut rules about its application and release should be known by all the theatre staff. An Esmarch bandage should be restricted to the thigh. There is no place for below-knee tourniquets, and on the upper limb only a pneumatic cuff should be used A tourniquet should never be put directly on the skin but over towelling The maximal period of application is 2 hours, and 1 hour should rarely be exceeded A distinct contraindication is in peripheral vascular disease and the elderly, when limb vessels may fracture or thrombose For emergency use with severe arterial bleeding a tourniquet should be applied as early as possible after the injury The patient should be given the highest priority for transportation to the nearest hospital, and the time of application should be written on the patient's forehead and the receiving-room informed directly of its presence If the patient is shocked from hæmorrhage the tourniquet should not be removed before a plasma-expander, preferably blood, is already running in It is folly to compromise a life in an effort to save a limb

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[1] The Collected Papers of Joseph Lister vol. 2 Oxford, 1909
[2] The Apologie and Treatise of Ambroise Paré (edited G Keynes) London, 1951
[3] Pannett C. A. *Lancet* March 15 1958, p 585
[4] Spiegel J Lewin P *J Amer med Ass* 1945 129, 432
[5] Moldaver J *Arch Surg Chicago* 1954 68 136
[6] Wolff L. H., Adkins T F *Bull U.S Army med Dept* 1945, 87, 77

As with many other surgical devices a tourniquet properly used may save lives and limbs if used unthinkingly it may cause serious and irreparable damage

Iron Deficiency in Man

IRON deficiency is one of the commonest debilitating diseases affecting man It may be due to chronic blood-loss (as from hæmorrhoids), to inadequate iron in a defective diet, to increased iron requirements (as in pregnancy), to defective iron absorption (as in steatorrhœa), and sometimes to imperfect utilisation The efforts of many interested workers have provided us with much quantitative information about iron absorption and metabolism JOSEPHS[1] has lately compared the four main methods of studying iron absorption The original balance method determined by chemical estimation the amount of iron ingested and the amount recovered from the fæces This method, which was used by MCCANCE and WIDDOWSON[2] many years ago, is difficult because the technique of estimation needs exceptional care and all clinical balances need great vigilance, but it has the advantage that the observations can be continued for as long as is necessary and can be repeated The balance technique utilising radioactive-iron isotopes incorporated into iron salts or food is much easier but cannot be repeated on individual patients because there is a limit to radioactive doses Another method is to estimate iron absorption from the rise in hæmoglobin in the patient's blood the implied assumption that all absorbed iron is used only for hæmoglobin formation may not always be correct, but NEERHOUT et al[3] showed that in dogs 95% of absorbed isotope-tagged iron is present in the red-cell mass fourteen days after feeding The last method is to follow changes in serum-iron after giving a test dose JOSEPHS considers that results from this method are of only limited value, a good rise of serum-iron level after the test dose clearly indicates good absorption, but the reverse is not necessarily true JOSEPHS concludes that the chemical iron-balance method, for all its difficulty, has given results that constitute the standard for judging other methods, and it is by this method and the isotope-balance techniques that most of our information has been acquired

GUBLER[4] pointed out that the average adult human body contains about 4 5 g of iron Hæmoglobin accounts for 73% of this iron and myoglobin in muscle tissue for 3 3%, "storage iron" (ferritin, hæmosiderin, and "unaccounted iron") present mostly in liver, bone-marrow, and spleen comprises 23 5%, and the remaining 0 2% is "parenchymal" iron—cytochrome, catalase, peroxidase, found in all tissues In the normal adult 27–28 mg of iron is released daily from the breakdown of hæmoglobin, and all, except about 1 mg, is utilised again for fresh hæmoglobin formation The normal adult excretes about 1 2 mg of iron daily, and the normal woman additionally loses iron in the menstrual loss at the rate of 1 mg daily, so the iron requirement of women is double that of men In pregnancy no iron is lost in the menses, but an average of 2 7 mg daily has to be provided for the fœtus During the period of growth from infancy to adolescence larger amounts are needed since expansion as well as excretion has to be covered, and for the first twenty years of life an additional 0 3–0 6 mg daily must be provided GUBLER cites the National Research Council's estimate that, allowing for only 10% absorption of iron from the food, daily amounts of iron needed are for infants 1 mg per kg body-weight, for children 0 6 mg per kg, for adult men 10 mg, for adult women 12 mg, and for pregnant women 15–20 mg CARL MOORE[5] has stated that the normal adult diet in the U S A yields about 12–15 mg of iron daily It is clear that most women in the reproductive period of life have a precarious iron balance, and undue menstrual loss or poor diet inevitably produces a negative balance which eventually shows as iron-deficiency anæmia Conditions such as diarrhœa, infection, and steatorrhœa will also soon cause excessive iron loss But in men, and in women past the menopause, iron-deficiency anæmia nearly always denotes blood-loss, and the cause has to be diligently sought Dr Bedford's paper in our present issue shows that in old people anæmia from slight bleeding into the alimentary canal may be far commoner than is supposed

Accordingly it is obvious why iron-deficiency anæmia is so common Fortunately we have several ways of giving iron efficaciously, and iron alone is adequate treatment for uncomplicated iron-deficiency anæmia Apart from vitamin C, there is no firm evidence that the addition of vitamins, such as those of the B complex, or of trace metals or liver fractions makes any difference to the response On the other hand, there are many recommended iron preparations, and the fact that new ones keep appearing indicates that we still lack one that is completely satisfactory One of the main difficulties is that oral iron preparations are liable to cause troublesome gastrointestinal side-effects such as nausea, heartburn, diarrhœa, or constipation These side-effects often cause the patients to stop taking their pills, and, since they sometimes fail to confess unless directly questioned, the physician may regard them as "refractory" cases and resort to intramuscular or intravenous iron preparations There are various ways of minimising these side-effects The most usual is to insist that the iron tablets are taken with meals, but **FRANKLIN** et al [6] point out that this reduces the effectiveness of the iron preparation Another way has been to use organic instead of inorganic iron salts—e g, ferrous gluconate or succinate instead of ferrous sulphate **O'SULLIVAN** et al [7] showed that the relative freedom from side-effects of the organic salts was due to the fact that they contain less iron Where equal iron doses were given under comparable conditions, all these ferrous salts were about equally effective, and the troublesome side-effects affected about 13% of their patients, whichever iron preparation was used The ferric salts are better tolerated so long as the dose is kept down, but they are definitely less effective and treatment takes longer

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[1] Josephs, H W *Blood*, 1958, 13, 1
[2] McCance, R A Widdowson, E M *Lancet*, 1937, ii, 680
[3] Neerhout R C, Armstrong, D H, Schulz, J, Smith, N T *Amer J Dis Child* 1958, 95, 126
[4] Gubler, C J *Science*, 1956, 123, 87
[5] Moore, C V *Amer J clin Nutr* 1955, 3, 3

FRANKLIN et al [6] have lately described their results with an oral chelated-iron compound Chelation has been used before, but mainly to try to prepare safe and effective parenteral iron drugs **WILL** and **VILTER** [8] used sodium iron edetate, a chelated compound, as an oral substitute for ferrous sulphate, they found that it released iron satisfactorily and was notably free from unpleasant side-effects, but interchange between iron and calcium occurs with this compound, and, though the effect is small, it is probably best avoided The complex used by **FRANKLIN** et al was an iron choline citrate containing 12 5% of elemental iron—about the same as in ferrous gluconate (11 5% Fe) This compound was put up in tablets containing 40 mg of iron, and three to six tablets a day were given *between* meals In 18 patients receiving 160 mg Fe daily as iron choline citrate, the average hæmoglobin gain per day was 0 14 g per 100 ml —which is of the same order as the figure obtained by **O'SULLIVAN** et al for ferrous gluconate or sulphate None of these 18 patients complained of gastrointestinal upsets A larger group of 88 patients in hospital were given two tablets three times daily (240 mg Fe) and 6 complained of mild nausea, diarrhœa, or constipation, the therapy was continued despite these symptoms, and they soon disappeared Animal experiments indicate that the choline citrate complex was less toxic than ferrous sulphate or gluconate This chelated-iron complex may well have therapeutic possibilities, and enable us to reduce still further the number of patients who have to be given parenteral iron How widely iron choline citrate is used may depend on its cost Ferrous sulphate is very cheap, ferrous gluconate costs about five times as much as sulphate, ferrous succinate and fumarate still more Parenteral treatment is still considerably more expensive than oral treatment. It would clearly be uneconomic to substitute an expensive iron compound just to eliminate the side-effects that involve 13% of patients, but chelated iron may reasonably be kept in reserve for intolerant patients

Every doctor sees patients with iron-deficiency anæmia, and, nowadays, every doctor can have a scheme for treating them satisfactorily Most of the patients will respond to oral iron, and, as **O'SULLIVAN** et al showed, relatively small doses yielding about 210 mg elemental iron a day are sufficient, this means three tablets of 0 2 g ferrous sulphate or four tablets of 0 3 g ferrous gluconate daily The 10% or so of patients who get gastrointestinal upsets with these drugs can be given ferrous fumarate or succinate or larger doses of a ferric hydroxide preparation, though they may still get symptoms with these alternatives These difficult patients and those who do not respond to oral iron can be treated with the intramuscular iron-dextran compounds, which have gained deserved popularity **GRIMES** and **HUTT** [9] have shown that almost all the absorbed iron given in this way is utilised for hæmoglobin formation, but only 60% of an injected dose is absorbed quickly, the remainder being absorbed slowly over a period of perhaps four weeks **EVANS** and **RAMSAY**,[10] studying absorption of iron-dextran in pregnancy, found evidence of maximum absorption from the injection site in ten to twenty days, 80% absorption within three weeks, and residual absorption for as long as six months These results indicate that intramuscular iron-dextran is an efficient way of giving iron, but, to allow for the relatively slow absorption of 40% of the injected dose, it is customary to allow 40 mg of iron for every hæmoglobin deficit With such a scheme every patient with iron-deficiency anæmia should respond to treatment, if they do not the diagnosis may not be correct, and the patient should be referred to the nearest suitable clinic without delay

Annotations

STREPTOCOCCAL SAGA

THE severity and frequency of streptococcal respiratory infections seem to be slowly declining, at any rate in Great Britain, and the decrease is especially noticeable in regard to rheumatic fever Much useful epidemiological information has been derived from American studies on the prevention and treatment of streptococcal pharyngitis, and in particular on the transmission of group-A streptococci [11], and some of the difficulties which may hinder attempts to eradicate epidemic strains of streptococci by the use of penicillin prophylaxis have recently been discussed by Frank [12] In the American army extensive bacteriological studies have been carried out in a streptococcal-disease-control programme, prompted chiefly by the high incidence in this population of rheumatic fever, following upper respiratory infections with group-A streptococci This incidence—about 3 per 100 streptococcal infections [13] is considerably higher than would be expected in, say, British schoolchildren similarly convalescent Holmes and Williams [14] at the Streptococcal Reference Laboratory, Colindale, have made a valuable long-term investigation of streptococcal disease in a large residential home for children

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[6] Franklin M Rohse W G, de la Huerga J, Kemp, C R *J Amer med Ass* 1958, 166 1685

[7] O Sullivan D J, Higgins, P G, Wilkinson J F *Lancet* 1955, ii, 482

[8] Will, J J, Vilter, R. R. *J Lab clin. Med* 1954, 44 499

[9] Grimes A J Hutt M S R *Brit med J* 1957, ii, 1074

[10] Evans, L A J Ramsay, N W *Lancet*, 1957, ii 1192

[11] Perry W D Siegel, A C Rammelkamp C H, Wannamaker, L. W, Marple E C *Amer J Hyg* 1957 66 85 96

[12] Frank, P F *U S Forces med J* 1958 9 543

[13] Rammelkamp, C H, Wannamaker, L W, Denny, F W *Bull NY Acad Med* 1952, 28, 321

[14] Holmes, M C, Williams, R E O *J Hyg, Camb* 1958, 56 43

These workers studied 300–500 children living in a large Dr Barnardo's Home for thirty months, giving a total of about 12,500 child-months During this period 473 sore throats were observed, of which 60% were streptococcal (group A) The overall attack-rate (1 9 streptococcal throat infections per 100 children per month) was very similar to that reported by Dingle et al [15] in a study of American families living at home (1 2 per 100 person-months), but the incidence of a streptococcal sore throat in the children increased with age, "of the illnesses diagnosed as 'sore throat' the proportion yielding streptococci increased from about 34% in the 1–2-year-old group to about 74% in the children over 10 years old" *The influence of tonsillectomy on severity of streptococcal* infections was found to be negligible Most previous workers found a lower *throat* carriage-rate in tonsillectomised convalescent children than in others, and in previous work Holmes and Williams [16] found that this applied to both the throat and the nose carrier state, but in this latest survey they found that, while throat carrier-rates in convalescence decreased more rapidly when tonsils were out than when tonsils were in, the *nasal* carriage-rate was much higher in the tonsillectomised children both on admission and during convalescence This is a puzzling point, which is related to the second part of the survey

Here an attempt was made to define the potential sources of infection among the incubating, the convalescent, and healthy carriers, classified as nasal or throat type No similar study has been reported, and Holmes and Williams have devised a simple objective way of relating cases of sore throat to their recognised infected contacts They were able to relate 94 out of 205 sore throats to their probable or possible contacts, of these two-thirds were heavy nasal carriers of streptococci, and the remainder about equally light nasal or throat-only carriers This confirms the importance attached by Hamburger et al [17] to nasal carriers as sources of infection Holmes and Williams point out, however, that the importance of *healthy* carriers may have been overstressed, since both persons incubating streptococcal disease and convalescent carriers could also reasonably be incriminated as sources of infection, the numbers in each category equalling those of healthy carriers responsible for spread No cases of rheumatic fever were observed among several hundred cases of streptococcal illness, nor was acute glomerulonephritis found despite 49 cases of infection with type-12 streptococcus It looks as if the nature of streptococcal disease is undergoing a slow change, or at any rate is showing widening variation, which studies like this one help to define We look forward to the concluding chapters of Holmes and Williams' saga

LONG-ACTING COUGH SUPPRESSANT

IT is often desirable to ensure the slow and steady release of an active drug from the gut The simplest way of doing this is to take the drug after food A recent valuable innovation is the use of capsules each containing the drug in the form of a large number of microspheres coated with a digestible wax in varying thicknesses [18] A new principle has now been employed—the integration of the active drug in an ion-exchanging-resin complex It is claimed that a drug given in this way is released from the resin at a slow and steady rate which is independent of the environmental pH and of enzyme activity [19] A preliminary report of a long-acting cough suppressant, in which dihydrocodeinone and the anti-histamine phenyltoloxamine are combined in a sulphonic resin complex, has been published [20] The evaluation of cough suppressants is not always easy, and perhaps greater objectivity in the conduct of the trial might have strengthened the author's case But the preliminary results do suggest that this is a useful new approach

ZIRCONIUM GRANULOMAS

LAST year we recorded [21] the appearance of a new and unique dermatological entity, first described by Rubin et al in Chicago [22] [23] This consisted of dusky reddish-brown discrete papules, 1–4 mm in diameter, which were closely set in the domes of the axillæ and more sparsely placed at the periphery Histologically there were granulomas in the corium, composed of epithelioid cells and Langhans giant cells surrounded by lymphocytes in typical tuberculoid pattern There was no delineation of tubercles of the sort seen in sarcoidosis, and no evidence of necrosis Foreign bodies could not be detected by polaroscopic examination The infiltrate lay along the course of blood-vessels It was noted that these novel lesions appeared after the use of deodorant sticks which contained sodium zirconium lactate in addition to the commonly used ingredients Rubin et al were uncertain of the cause of this granulomatous eruptions but thought that the linear distribution of the lesions suggested razor abrasions

Further cases were soon described, always arising after the use of a deodorant containing zirconium salts But zirconium seemed non-toxic,[24] and there were no recorded instances of its having proved harmful in industry In biopsy specimens from the axillary lesions no zirconium was found, even by such refined means as X-ray fluorescence and emission spectrometry [25] Many alternative causes were suggested, such as foreign-body reactions to the lipid vehicle of the deodorant stick [26] and inflammation as the result of extravasation of apocrine sweat [27]

Shelley and Hurley [28] have contributed a well-integrated review of 64 cases previously reported and 6 of their own They find the clinical signs as well as the histological changes in the dermis to be strictly uniform and diagnostic Most cases were in women, and most of them shaved their axillæ No one brand of deodorant stick was responsible The eruption might follow a solitary use of the "zirconium stick" or appear only after it had been used daily for months

Shelley and Hurley then conducted experiments to elucidate the role of zirconium They instructed 30 healthy male volunteers to rub a standard commercial stick deodorant, containing 5% zirconium, vigorously into their left axilla every morning for five minutes A zirconium-free but otherwise identical stick was rubbed daily into the right axilla for the same period Both axillæ were closely shaved every other day None of the men had previously used zirconium stick

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21 *Lancet*, 1957, i, 519
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27 Saunders, T S *ibid* 1957, 76, 619
28 Shelley, W B , Hurley, H J *Brit J Derm* 1958, 70, 75

deodorants The test period lasted ten weeks, biopsies were taken from both axillæ in every subject After a month 1 volunteer developed an eruption in the left axilla, which clinically and histologically was identical with the clinical cases of axillary granuloma Applications were stopped after eight weeks, and no treatment was given The confluent papules, lying linearly as if developed in a razor cut, slowly subsided over the subsequent five months The opposite axilla showed no clinical or microscopical changes In 3 other subjects there was a transitory inflammatory papular response, which was not granulomatous, in the left axilla There was no reaction in the opposite axilla of these 3 or in either axilla of the remaining 26 subjects The concentration of zirconium was then changed and hexachlorophene, perfume, and carbitol were omitted from the stick. 1 subject out of a further 20 showed typical granulomas when 10% sodium zirconium lactate in a plain sodium stearate soap vehicle was used The opposite axilla failed to produce granulomas after a ten-week test with a stick containing 0 5% zirconium Patch testing in the 2 who reacted to the zirconium stick, as well as in 20 controls, failed to give any reaction Intradermal testing of the 2 reactors showed a unique granulomatous response—in 1 case to a dilution of 1/10,000 and in the other to 1/1000 No similar reaction was seen in control subjects even with concentrations as high as 1/100 The granulomatous reaction is specific to the zirconium element, for zirconium chloride and zirconium nitrate produced identical lesions in the 2 reactors Injections of 1/1000 beryllium sulphate and colloidal silica failed to produce a response in any subject, and in the 2 hypersensitive subjects the use of aluminium stick deodorants led to no granulomatous reaction

From these exhaustive tests Shelley and Hurley concluded that the granulomas were the direct result of a specific allergic hypersensitivity to zirconium They proceeded to test their observations on 4 patients with typical deodorant granulomas in their axillæ In each case their responses were identical with those of the 2 hypersensitive volunteers

In the past a number of granulomas have been thought to be allergic in origin, but this is the first time that the introduction of extremely small amounts of a pure substance has produced an allergic epithelioid granuloma in man. It opens up an entirely new field of immunological response with granuloma production May the reaction in the Mitsuda and Kveim tests be due to traces of highly specific allergens contained in extracts from lepra bacilli and sarcoid tissue respectively? It may soon be possible to discover the antigenic substance in the tubercle bacillus responsible for the tuberculoid granulomas—though here the amount of material needed to produce the reaction is appreciable, whereas the amounts concerned in zirconium granulomas are too small to be detected by analysis The method might be applicable in the diagnosis of pneumoconiosis or the demonstration of specific hypersensitivity in patients with beryllium, silicate, or tattoo granulomas There is no theoretical reason to suppose that the dermis alone becomes sensitised The ultimate mechanism must surely be chemical, and it would be interesting to learn how zirconium affects enzyme reactions in the skin Shelley and Hurley's work may therefore be of wide significance, they suggest that the detection of minute quantities of specific sensitising agents may lead to the discovery of the cause of sarcoidal granulomatous diseases of hitherto unknown origin

In this country we are unlikely to see any of these axillary lesions, though some possible cases have been suspected here, because zirconium has already been withdrawn from use in deodorants The stimulus of Shelley and Hurley's neat investigation remains

OCULAR LESIONS IN ONCHOCERCIASIS

ONCHOCERCIASIS has come to be regarded as one of the major blinding affections It is said that in some villages in Nigeria and the Gold Coast a tenth of the inhabitants have lost their sight from this cause Onchocerciasis has been known for some sixty years, and ocular lesions, first reported from Guatemala in 1915, were stressed by Hisette in 1932 in a classical account of the affection as seen in the Belgian Congo

The anterior third of the corneal stroma and the anterior chamber are invaded by microfilariæ travelling over the conjunctiva or along the subconjunctival plane, the iris itself may become infiltrated, though apparently the lens is spared The living microfilariæ seem to be well tolerated, and it is not the toxin of the organism, but the decomposing dead organism, which produces the irritative reactions in the cornea and iris Considerable interest centres on the fundus lesions that have been recorded in onchocerciasis since they were described first by Hisette, and subsequently by Bryant in 1935 [1] and by Ridley in 1945 [2] These lesions take two forms, one simulating the non-specific inflammatory reaction seen in chorioretinitis and the other—described by Ridley as a "hypothetical combination of choroidal sclerosis with retinitis pigmentosa"—involving the macular area and the disc, which shows secondary optic atrophy

In the earlier accounts the ocular lesions were described as complications of longstanding and severe affections But from a recent symposium held by the Royal Society of Tropical Medicine and Hygiene [3] it is clear that slight conjunctivitis, and possibly slight corneal lesions, may be a pointing sign in even mild infections The corneal lesion consists of opacities usually most noticeable near the limbus, with a tendency to spread across the cornea into the interpalpebral area In severe cases these opacities can become confluent, and only exceptionally do they become vascularised The causal relationship between these corneal reactions and the microfilaria of onchocerciasis can be established by slit-lamp examination—as is stressed by Choyce [4] in his criticism of the view expressed by Rodger,[5] who doubted the specificity of onchocercal keratitis Choyce also remarks on the difficulty of regarding onchocerciasis as a blinding affection, since only exceptionally is there any substantial reduction of vision from these corneal lesions, though the occasional case of iritis with secondary glaucoma may run a severe course The fundus lesion, which has attracted so much attention, was observed by Ridley in 12 of his 51 cases at Funsi in the Northern region of the Gold Coast In the Cameroons Choyce saw the fundus lesion described by Ridley, but he does not believe that this is caused by onchocerciasis, if only because microfilariæ do not travel by either the blood-stream or the central nervous system Microfilariæ have apparently not been found in the retina, and the fundus lesion does not appear to have been observed in Central and South America, where onchocerciasis is also prevalent He regards the fundus lesions as examples of the different stages of the dominantly inherited generalised choroidal sclerosis described by Sorsby [6]

If this is correct, there is little to justify the growing reputation of onchocerciasis as a blinding affection.

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[1] Bryant J *Trans R Soc trop Med Hyg* 1935, 28, 523
[2] Ridley, H *Brit J Ophthal* 1945, suppl 10
[3] *Trans R Soc. trop Med Hyg* 1958, 52, 95–134
[4] Choyce, D P *ibid* p 112
[5] Rodger F C *Brit J Ophthal* 1957, 41, 599
[6] Sorsby, A *ibid* 1939, 23, 433 Sorsby, A., Davey, J B *ibid* 1955, 39, 257

Whether this disease is indeed a significant cause of blindness is unlikely to be decided by merely descriptive accounts of the lesions The epidemiologist and the geneticist have clear criteria for determining whether a particular lesion is infective or genetic in origin, and it should not prove particularly difficult to establish the nature of the fundus lesion associated with onchocerciasis

ANTIBODY-ANTIGEN REACTIONS OBSERVED BY FLUORESCENCE

All interested in the infections which befall man and animals have wanted to find out where the invading microorganisms are distributed in the host It is known that when the respiratory tract is infected the microorganism can be isolated from this situation, it is known that, as the patient recovers, antibodies are produced in areas far distant from the primary lesion, and it is believed that the areas producing the antibody must have been stimulated directly by the infecting agent or its products What tissues distant to the obviously infected site have been in contact with the agent? The most fruitful experiments designed to answer this and related questions have depended on the use of fluorescent-labelled antibody [1] [2] By this method the globulin fraction of a hyper-immune serum is conjugated with fluorescein isocyanate, this labelled antibody combines with the appropriate antigen, and this antigen-antibody reaction can be seen because of the fluorescence

Coons et al, using this method as a histochemical stain,[3] demonstrated the cellular distribution of pneumococcal polysaccharides injected into the mouse, the distribution of rickettsia of epidemic typhus fever and Rocky Mountain spotted fever injected into cotton rats, and the distribution of mumps virus injected into monkeys [4] In this work the labelled antigen was used for staining sections Moody et al [5] used immune labelled globulin to identify *Malleomyces pseudomallei* on films, as would be expected from knowledge of the close antigenic relationship between *M pseudomallei* and *M mallei*, serum made from one type stained both organisms This work has been extended by Thomason et al [6] to show the position of various antigens on organisms of the salmonella group They have shown that the Vi antigen of the typhoid bacillus may not be evenly distributed over the surface—a result that others had predicted from various agglutination tests They also showed that an antigen known to be present in loosely related salmonella showed itself in stained preparations as fluorescent dots round the periphery of the bacterial cell This technique has not been found satisfactory for demonstrating salmonella in fæcal smears,[7] but may be of value for demonstrating shigella [8] Similar tests have been used to distinguish between *Entamœba coli* and *Entamœba histolytica* [9] These experiments yielded additional evidence that the reaction between antigen and antibody is specific

Last year Hobson and Mann [10] labelled specific antisera prepared with organisms isolated from the rumen of calves, and found it possible to identify many organisms by mixing on a slide small amounts of rumen contents, buffered saline, and labelled antiserum, placing a cover slip on the preparation, and viewing Though it was possible to obtain results by direct microscopy, a better picture was obtained photographically These workers state that naturally occurring fluorescing materials were present in rumen contents and occasionally in objects which absorbed conjugated antiserum, but with experience it was possible to distinguish these from the specific organisms both by morphology and by colour of the fluorescence

Whitaker et al [11] used labelled antibody to investigate fæces which had been collected from an outbreak of infantile gastroenteritis due to *Escherichia coli* 0 127 Films on slides were made from fæces, rectal swab, and bacterial cultures, these were stained with labelled antiglobulin, and a photograph was taken It was found that all fæces positive by routine bacteriological test were positive by the new technique In addition 61 specimens from cases reported as negative were tested and 39 were found to be positive by fluorescence, all these cases had been treated with neomycin, and it was suggested that the fluorescence showed the presence of organisms killed by the antibiotic

Globulin-fluorescein and globulin-rodamine conjugates have been used in the investigation of carcinogenesis [12] and the identification of tumour cells [13] Normal tissues react with globulin prepared both from the homologous species and that prepared from many different animal species, malignant tumour cells show no reaction This effect, which is non-specific, is believed to be due to physicochemical characteristics of globulin, allowing interactions between globulin and normal tissues that probably differ fundamentally from antigen-antibody reactions already described

In the elucidation of bacteriological and allied problems labelled globulin gives an answer very similar to that obtained from specific antigen-antibody reactions brought about by other methods, and difficulties which arise in such reactions are likely to arise with the newer technique It is known that many bacterial antigens are to be found in widely differing species of organisms, and in some organic extracts—possibly plants Obviously a fluorescent body in mixed material such as fæces cannot yet be unhesitatingly accepted as diagnostic of a particular bacterium or virus Another difficulty is that labelled sera may impart fluorescence to tissues to which they are not known to be related Such non-specific reactions may be reduced by absorbing the serum with minced kidney, and it might be necessary to absorb serum with human tissue if the serum were to be used for the diagnosis of human material By present technique the fluorescent method is time-consuming and unlikely to give a reliable answer more quickly than the conventional methods, but simpler techniques will no doubt be introduced, and this new method may eventually prove of value to the routine bacteriologist The staining of tissues with labelled normal globulin may become a valued method for the differentiation of malignant cells

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Special Articles

POSTMATURITY

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THE nature and management of "postmaturity" has always been uncertain and difficult (I use inverted commas because the term has a different meaning to different people) Until very recent years the student and the practitioner have had little or (perhaps better) no guidance on it

As Ballantyne and Browne said in 1922, the problem was as old as the hills But now that childbirth has become progressively safer, what was formerly a minor trouble has gained in relative importance

Over the past fifty years three distinct policies seem to have been evolved, and each still has its adherents The original policy (A)—laissez-faire, or leave it to Nature—was based partly on clinical experience but partly on lack of understanding Dissatisfaction with this plan was followed by policy B—induction of labour *as a routine* so as to avoid the mechanical difficulties that may accompany birth of a large "postmature" baby The argument used was that it is better to induce labour unnecessarily many times than to run risks unnecessarily in a few cases At the moment, however, support for this policy seems to be on the wane, and the dispute lies for the most part between believers in policy A and those who accept the latest suggestion—namely, that the real danger lies in placental insufficiency or inefficiency—and accordingly act upon policy C

Two statements made some years ago seem to me to epitomise the problem Reynolds (1938) said

> "Postmaturity has peculiar difficulties as a subject for discussion, since we have at present no definition of what we mean Fœtal development, well above the average as regards size, weight, ossification, &c, is not necessarily a result of prolonged gestation, just as immaturity is not synonymous with prematurity"

Similarly, in America, Adair (1940)

> "There are individuals who persistently delay in the natural onset of labour, each pregnancy being of longer duration than the average normal, the fœtal size appearing to have no bearing on the phenomenon The fœtus may be oversize, of normal or below normal weight"

Any department of obstetrics can easily produce evidence that a large healthy baby can be born before the calculated expected date, and that one of normal weight or less may arrive in a perfectly healthy state much later

"The Exact Date"

Of course there is no exact time for gestation Indeed, it is a reflection on current teaching and intelligence that the statement is necessary at all For is there an "exact" height or an "exact" weight, or a uniform or "exact" rate of urinary secretion, gastric digestion, or (for that matter) cerebration? Why, therefore, should there be an "exact time for gestation"? Naturally, there should be a recognised *average* time for gestation, but in its calculation there must be as many variants on one side of the line as on the other, and most of these variants must be physiological and not pathological Hence no woman in her pregnancy can be given an exact date for the onset of labour, and any policy must be wrong if it involves routine interference with all pregnancies prolonged beyond a calculated period If there is no "exact date", management of the condition must vary from patient to patient

The Three Policies Examined

At this point, therefore, the road divides Those who insist on some inflexible rule need read no further The following comments on the three policies are made only to those who can agree that a precise routine is impossible

Policy A—leaving the onset of labour to Nature—has certainly much to commend it It allows the obstetrician a relatively easy and peaceful life The anxieties of the patient and her relatives can usually be allayed by pleasant platitudes or by citing the experience of many others who faced a similar predicament Every woman is likely to be familiar with the vagaries of an oven, and indeed this homely comparison should not be dismissed too readily as foolish and misleading All who have practised obstetrics will have met, as Adair suggested, many instances of women whose babies, of average weight and development at birth, consistently arrived either before or after the calculated expected date What is overlooked by those who follow rigidly the plan of laissez-faire is that variations from the normal are not extremely rare and can often be detected by clinical observation Such variables include the age of the woman and the state of her general health, pre-eclamptic toxæmia (even in the mildest degree), her physical structure and that of the bony pelvis, and the estimated size and maturity of the fœtus Strict adherence to policy A cannot be justified in the light of present-day knowledge, slight though this is

Policy B postulates that after a woman passes the date when labour is expected there is a steadily increasing risk that the fœtus will become unduly large and hence that its delivery may be difficult or dangerous This risk, I agree, is real, but it certainly does not justify a policy of *routine* termination of pregnancy *x* days after the "exact" day

We are nowadays told, on apparently incontrovertible evidence, that one can forecast accurately whether the fœtal head will pass through the bony birth-canal, and, if so, whether it will do so easily or with difficulty, but those who say this do not so much as hint that similar methods of observation can be applied to the "postmature" fœtus If it is possible to diagnose minor degrees of disproportion before the "exact" calculated date, it must also be possible to do so when this day has passed Either all efforts in this direction are valueless or they are valuable If they are valueless, then by all means accept policy B, but if they are valuable a routine induction of labour to avoid disproportion is unjustified The argument is absolute

In actual fact, the fœtus may be unduly large *before* the "exact" date, either fortuitously or because the mother has diabetes Fœtal size may also be influenced by rhesus incompatibility or by congenital abnormality Policy B does not take account of these possibilities Nor does it take account of women whose pregnancy seems to be consistently prolonged over the calculated 280 days, or of the fact that routine termination of pregnancy is bound to result in some premature births Its advocates forget that induction of labour, as a deviation from the normal, *must* have an incidence of morbidity Undoubtedly there are advantages in policy B, but its adoption *as a routine* cannot be correct

Policy C, in principle, is much the same as policy B—substituting the pathological bogy of "placental insufficiency " for the anatomical bogy of the large postmature fœtus Nobody will dispute that placental insufficiency occurs and is highly dangerous to the fœtus, and it is likely to be worst in women who have passed their expected date of delivery Accordingly routine induction of labour is recommended at some stated time—about which (very naturally) there seems to be no agreement—after the calculated " exact " date This policy, however, appears even more illogical than policy B, for, whereas some attempt at least can be made to assess the size of the fœtus in utero, at present there are no means whatever of assessing placental efficiency Figures have been produced to show that adoption of policy C has been followed by improvement in perinatal mortality, but the extent of the improvement must be compared to an improvement on a national basis, and perhaps the improvement in any particular department or centre may have been from " not so good " to " good " rather than (as is implied) from " good " to " very good "

We do, of course, know something about the circumstances likely to impair placental efficiency Thus Baird (1957) has shown that, like other physiological processes, it is more likely to fail in women, especially primigravidæ, whose pregnancy occurs toward the end of the child-bearing period, and there is wide appreciation of the almost inevitable impairment of placental function in pre-eclamptic toxæmia (however mild), hypertension, or diabetes But Rooth and Sjostedt (1957) in Sweden, and later Bancroft-Livingston and Neill (1957) in Belfast, have failed to confirm the very foundations on which placental insufficiency has been related to postmaturity These two sets of workers go as far as to advise that the supposed association between the two conditions be abandoned, for independently they had been unable to confirm the findings of Walker, Turnbull, and others of a diminution of oxygen-saturation in the cord blood with increasing gestation Be this as it may, there is no justification for the adoption of any routine of management, as advocated in policy C

Suggested Management of Postmaturity

" Postmaturity "—i e , the prolongation of pregnancy beyond the calculated (exact) date—is important because it is so common Some invaluable clinical facts are available for its management, but very few people seem to try to take all of them into consideration

1 In the first place, policy A is dead There is no place at all for complete neglect, no matter how often Nature appears to be successful

2 Next, it must be accepted that there is no such thing as an " exact " duration of pregnancy The arbitrary calculated date is useful and necessary, and in the woman who is being watched because of mild pre-eclamptic toxæmia or hypertension it may be of vital importance In such cases the pregnancy must be terminated

3 If the fœtus is large—as may happen either in health or through disease—appropriate action should be taken at the appropriate time Excessive size may be suspected by clinical observation either before, at, or after the calculated " exact " date

The suggestion has been made (Wrigley 1946) that, though an unusual increase in the size of the fœtus can be suspected by most observers, additional help would sometimes be obtained by noting the changing relationship between the bulk of the fœtus and the amount of the liquor amnii With increasing maturity the cavity of the uterus appears to be occupied almost wholly by the fœtus But it was emphasised that such findings could only be assessed with any accuracy if each patient was examined on each occasion by the same pair of hands—which is seldom done in the existing clinic or mass examination system With increasing maturity there is increasing muscle tone in the fœtus, and its appreciation may be helpful Mistakes are inevitable, for occasionally a small baby is truly postmature, and a large baby can equally well exhibit all the characteristics of prematurity

This suggestion, when first made, was criticised as esoteric, which was hardly just

4 As term approaches, every effort must be made to try to decide the " maturity " of the fœtus, but each case must be judged independently If at the expected date of confinement the patient appears in perfect health and the fœtus appears to be *small*, I would recommend that the case should be watched—but watched by the same person I would make an exception for the elderly primigravida, for whom labour should be induced

If at the expected date of confinement the size of the fœtus seems to be *normal*, the case can be watched again, but probably not for so long In reaching a decision, consideration would be given to factors such as the woman's age and parity, her height and build, and the shape and structure of her pelvis

If at term the fœtus appears without doubt to be *large*, and therefore almost certainly " mature ", or even postmature, labour should be induced

5 Such a policy avoids routine, and in consequence much unnecessary induction of labour It makes use of knowledge that is readily obtainable It takes into account the vital importance and influence of such diseases as pre-eclampsia, hypertension, diabetes, and rhesus incompatibility, and of the variable efficiency of the physiology of gestation in the later years of the childbearing period

Most important is an individual assessment of each case—individual in that every patient who passes her calculated date of confinement is observed by the same obstetrician

The adoption of the plan just outlined results in very few patients being induced for " postmaturity " During the years 1956–57, the obstetrical department at St. Thomas's Hospital delivered 1600 babies with a perinatal mortality of 34 5 per 1000 No fœtal perinatal death in this series was due to intracranial injury

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REGIONAL HOSPITAL BOARDS AND BOARDS OF GOVERNORS OF TEACHING HOSPITALS

THE following doctors have been appointed or reappointed to the boards They will hold office till March 31, 1961 New appointments are indicated by an asterisk

REGIONAL HOSPITAL BOARDS

Newcastle —R V Bradlaw, David Dickson
Leeds —P J Moir, * E W Jackson
Sheffield —E C Cordeaux, J G McCrie, G C Wells-Cole
East Anglia —A J R F Johnson, J V Morris
North West Metropolitan —Sir Harold Boldero, Horace Joules, J B S Lewis, * Annis Gillie
North East Metropolitan —* C Allan Birch
South East Metropolitan —J R H Turton
South West Metropolitan —* G W Garland, * Ivor MacDougall
Oxford —G T Willoughby Cashell, William Ogden, * A W Henderson

South Western—R G Michelmore, H L Shepherd, G Stewart Smith

Wales—David Kyle, Ivor Lewis, D E Parry-Pritchard, * Morgan Williams

Birmingham—J C Heather, Thomas McKeown, J J O'Reilly, * S R F Whittaker

Manchester—W I C Morris

Liverpool—D Brown

BOARDS OF GOVERNORS

St Bartholomew's Hospital—F C W Capps, Sir James Paterson Ross

London Hospital—H B May, J Stanley Thomas, V C Thompson, Clifford Wilson

Royal Free Hospital—Geraldine Barry, * C J Massey Dawkins

University College Hospital—C W Flemming, J D S Flew, K E Harris, * M L Formby

Middlesex Hospital—* C J B Murray, * Philip Wiles (till March 31, 1959)

Charing Cross Hospital—A Doyne Bell, Norman Lake, * P B S Fowler (till March 31, 1960)

St George's Hospital—Alastair Hunter, D Stark Murray, * Kenneth Robson

Westminster Hospital—F Dudley Hart, W E Lloyd

St Mary's Hospital—Joel Green, * R C Brown, * A J May, * Albert Neuberger and * E R Williams (till March 31, 1960)

Guy's Hospital—E R Boland, A H Douthwaite, Grant Massie, A Talbot Rogers, E G Slesinger

King's College Hospital—F S Cooksey, V F Hall, J H Peel, * A Fisher McMillan

St Thomas's Hospital—G H Bateman, R. W Nevin, J Forest Smith, R H O B Robinson

Hammersmith, West London, and St Mark's Hospitals—John McMichael, Charles Newman

Hospital for Sick Children—James Crooks, Alan Moncrieff, A P Norman

National Hospital for Nervous Diseases—Alan Kekwick, Sir Francis Walshe, * E A Blake Pritchard

Royal National Throat, Nose and Ear Hospital—Adam Gray, C Gill-Carey, * N Asherson

Moorfields Eye Hospital—R C Davenport, Sir Stewart Duke-Elder, C D Shapland

Bethlem Royal and Maudsley Hospitals—Sir Allen Daley, D L Davies, A Harris, F R Winton

St John's Hospital for Diseases of the Skin—F Ray Bettley, Brian Russell, * A D Porter (till March 31, 1959)

Hospitals for Diseases of the Chest—W E Lloyd, J G Scadding, Joseph Smart, Sir Geoffrey Todd

Royal National Orthopædic Hospital—H J Burrows, J A Cholmeley

National Heart Hospital—G W Hayward, G H Jennings, Paul Wood

St Peter's, St Paul's, and St Philip's Hospitals—A Clifford Morson, J G Sandrey

Royal Marsden Hospital—W A Mill, R W Raven, D W Smithers

Queen Charlotte's and Chelsea Hospitals—A C Bell, S G Clayton

Eastman Dental Hospital—F C Wilkinson, Katharine Lloyd-Williams

United Newcastle Hospitals—S W Davidson, J Gilmour, A G Ross Lowdon.

United Leeds Hospitals—H G Garland, A B Pain, R E Tunbridge

United Sheffield Hospitals—J L A Grout, J G McCrie, G L Roberts, C H Stuart-Harris, R B Zachary

United Cambridge Hospitals—Leslie Cole, Robert Ellis, D M T Gairdner, J S Mitchell, * R. I N Greaves

United Oxford Hospitals—G S Dawes, J B Pennybacker, * P R Allison

United Bristol Hospitals—C Bruce Perry, * R H Butcher, * A P Gorham, * G E F Sutton

United Cardiff Hospitals—A S Duncan, A Trevor Jones, R. G Maliphant

United Birmingham Hospitals—Arthur Beauchamp, J C Heather, Thomas McKeown, A B Taylor, A P Thomson, * A L d'Abreu

United Manchester Hospitals—William Chadwick, R W Luxton, Robert Platt, Walter Schlapp, * W F Gaisford, * H T Simmons

United Liverpool Hospitals—J M Leggate, * G R Ellis, * E L Rubin, * R Selby

REGIONAL DISTRIBUTION OF S H M O s

A CORRESPONDENT in our issue of May 17 (p 1071) asked whether the number of senior hospital-medical officers in each hospital region was known We are indebted to the Ministry of Health for providing the following figures (for various reasons, it is hard to state precise numbers, so round figures only are given)

Regional hospital board	*Whole-time equivalents at Dec 31, 1956*		*Actual number of S H M O s employed at Sept 1957 (full-time and part-time)*
Newcastle	90		140
Leeds	100		120
Sheffield	120		150
East Anglian	30		60
N W Metropolitan	140	580	1120
N E Metropolitan	110		
S E Metropolitan	120		
S W Metropolitan	210		
Oxford	60		120
South Western	110		160
Welsh	110		160
Birmingham	110		180
Manchester	120		200
Liverpool	70		110

It is important to note that the second column (totals for S H M O s in each region) includes those employed by boards of governors of teaching hospitals in each region, whereas the "whole-time equivalents" in the first column are for regional boards only The whole-time-equivalent figures for regional-board consultants were given in our issue of April 26 (p 907)

Greater Medical Profession

MEDICINE AND SPEECH THERAPY

MURIEL MORLEY
M Sc Durh, F C S T

DONALD COURT
M D Birm, F R C P

From the Department of Child Health, King's College, and the Royal Victoria Infirmary, Newcastle upon Tyne

UNTIL not very long ago the doctor practised virtually by himself Today he needs, and increasingly accepts, the help of many colleagues trained in disciplines different from his own Nurses, scientists, therapists, and technicians will all be necessary at some time for the proper understanding and treatment of patients

This multiplication of the techniques and the people involved in the care of the sick naturally complicates professional relationships The doctor finds himself to his surprise, and not always to his liking, the conductor of an orchestra in which many of the instruments are new and unfamiliar How should he respond to these new demands upon his patience and leadership? In an address to the Manchester Medical Society two years ago, T F Fox[1] said that the aim should be to create a "greater medical profession" in which everyone works to professional standards and experiences mutual professional respect Others, however, have advocated a subsidiary role for such colleagues and have encouraged them to accept registration as medical auxiliaries We have been thinking and working our way through this problem in relation to speech therapy, and we offer our experience as one way in which Dr Fox's general counsel is being applied

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[1] Fox, T F *Lancet*, 1956, ii, 779

This account also seems necessary since certain critical letters[2] suggest that medical ignorance of the nature of speech therapy and the work of speech therapists is more widespread than we had supposed

Concise definitions are always difficult, but if we regard a doctor as one who, when invited, cares for the sick and advises the well, we might accept the definition of a speech therapist as "one who cares for speech"[3] Her function is "to assist the person with a speech disorder to achieve speech which is intelligible, adequate for the life he leads, and without abnormality which might attract attention"[4]

Up to the present some 1000 therapists have qualified in this country, and approximately 70 are working overseas For three years they study phonetics, normal voice and speech, speech pathology and therapeutics, and enough anatomy, physiology, neurology, audiology, psychology, and psychopathology to start their rational understanding of speech development and speech disorders After this training in a recognised school of speech therapy and the passing of a professional examination they become licentiates of the College of Speech Therapists (L C S T) This college, set up in 1945, is the recognised qualifying body in speech therapy having authority to grant diplomas and develop professional registration in this country Speech therapists are therefore a profession in Dr Fox's sense of the term, since they "share a body of knowledge which they try to increase and transmit to new entrants, and a code of ethics, a set of standards which they try to follow in their work"

At present there are some 700 speech therapists in active practice in this country unevenly distributed between education and medicine A quarter are working in hospitals and three-quarters in relation to local education authorities

SPEECH THERAPISTS' CONTRIBUTION

What are they contributing to the community? First and foremost they are treating a wide range of speech disorders, in both children and adults, with practical awareness of the needs of those whose usefulness in the community is limited through a speech disability When we remember that at least 3% of all schoolchildren have a substantial disorder of speech, and when we list the disorders they present—dyslalia, dysarthria, articulatory apraxia, stammering, speech disturbances with deafness or with structural defects such as cleft palate, and other associated defects in the language field such as specific reading, spelling, and writing defects—the scope of the therapist's work is plain to see To the small speech-therapy unit of our own teaching hospital 307 patients were referred last year, 254 being children and 53 adults During the year, 329 were discharged with improved or adequate speech, the total number of attendances made by patients being 3547 But speech is no marginal activity for the growing child or the responsible adult, and speech therapy, by assisting them to achieve effective speech, often relieves associated personal and family anxiety and assists development of the whole personality It is not irrelevant at this point to compare this socially useful function with the reward that society offers in return The commencing salary of a speech therapist is £455 and the maximum possible for the head of a department is £815

NEEDS OF THE YOUNG PROFESSION

The treatment and study of speech disorders has developed widely in many countries in the last thirty years Speech therapy is therefore a young profession and is sensible of its immaturity What are its needs—in its own life and organisation—at the present time?

The central need is for more intensive inquiry into the basis of speech and the real nature of the defective development or breakdown which confronts us in the speech disorders While accepting research as one of the primary functions of universities, we would not advocate the immediate development of independent university departments of speech Such departments already exist in many universities in the United States, but it would be difficult and undesirable in this country to achieve them in one stage There must first be a small but sufficient number of speech therapists, with high technical ability and with academic training and judgment, to work in—and eventually lead—a limited number of university departments The necessary steps to train and use such therapists should be taken now, and we understand that at least two British universities are considering this approach

In Newcastle we have so far followed the pragmatic approach For the past ten years an experienced speech therapist, a neurologist, a pædiatrician, and an educational psychologist have studied the natural history and attempted a rational classification of developmental speech disorders The speech therapist is also a lecturer in the university department of education This association of people concerned in everyday treatment and speech inquiry has now reached the point where formal recognition by the university could be rationally considered The university subdepartment of speech which followed such recognition might find its first home in Medicine, in Psychology, or in Education Whatever the parent department, it would need working relationships with pædiatrics, otology, neurology, psychiatry, neurological surgery, and plastic surgery It would have a threefold charge—to continue and extend research, to offer graduate training to a limited number of selected teachers and speech therapists, and to work towards an undergraduate degree course in which speech was the principal subject

RELATION TO MEDICAL PRACTICE

We have let our hopes and ideas stretch out into the future What are the needs of speech therapy in relation to everyday medical practice?

In many cases working relationships between doctors and speech therapists do not exist at all, and must be created In others the doctor, though at hand, is ignorant of, or uninterested in, speech disorders and unaware of what the speech therapist has to offer No-one can do good work in continuing isolation, and there should always be a doctor, in hospital or in the school service, who is the committed colleague of the speech therapist—available for regular consultation and engaged in common inquiry

This will not be easily or rapidly achieved Doctors came before speech therapists, and to most doctors in family and hospital practice speech disorders seem a mere drop in the ocean of real and imaginary sickness which is their unending concern And since these disorders are never fatal, and the social disability they cause may escape the doctor's notice, his interest is not easily aroused Speech therapists, too, because of their isolation may sometimes be tempted to usurp the functions of the doctor and offer advice to the patient which is beyond their scope The language of medicine, with its powerful significance for the patient, may at times seem temptingly simple to those confined to a single and necessarily limited part of the field Yet the relationship must be one between professional colleagues, and to regard the speech therapist as a medical auxiliary is unreal and unworthy She is a specialist in her own field, and should be responsible for the diagnosis of the speech disorder and for deciding the type and length of treatment which will be most appropriate

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[2] *Brit Med J*, 1956, ii, 768, 884, 1000, 1058, 1118

[3] Wilkins, J L Report of Conference on Speech Therapy, p 3 London, 1948

[4] Morley, M E *Med Pr* Nov 1953, 230, 448

In the teaching hospital in Newcastle, after long experience and careful consideration, speech therapy has been established as a separate unit The senior speech therapist has become the therapist in charge, and medical responsibility is in the hands of five specialists who are available for consultation by the speech therapist and by the hospital administration and are responsible to the board of governors of the hospital The specialists are the senior consultants in neurology, otology, and plastic surgery, and the heads of the departments of child health and psychological medicine They are essentially the people who have shared in the practice and study of the subject in the past ten years, and we feel that it is best for inquiry, in this way, to precede organisation

The majority of speech therapists, however, are working with local education authorities, and they should find natural allies within the school health service Once again the problem is lack of enough doctors with sufficient understanding to work effectively with the speech therapist The teaching hospitals at present, and the university speech departments of the future, have an important and largely unfulfilled responsibility to present the subject to medical students, teachers, school medical officers, and family doctors

We are not blind to the time and effort and patience which the building of more effective relationships between doctors and speech therapists will require But neither are we in doubt about the need In this world of newspapers, cinemas, theatres, radio, television, and innumerable committees, felicity of language and excellence of diction are more necessary and more sought after than ever Education, medicine and speech therapy share the main responsibility here, and they would do well to face it in a more thorough way than has been attempted so far in this country

Yet in conclusion we would keep a sense of proportion This is a difficult subject and we are only at the beginning of understanding The problems of sincere and effective communication between men and nations are broader than speech We must be honest and precise about our ignorance We still have to find practical ways of developing research and increasing the numbers of speech therapists capable of university standards and responsibility On the other hand, we must avoid the monotonous multiplication of speech-therapy services for the sake of administrative tidiness or to enhance professional prestige Finally we recognise "that every addition to the number and variety of people concerned with a given patient increases the strain on the judgment and resolution of the person responsible for the patient's welfare" That person remains the doctor, and "to hold their own in the Greater Medical Profession doctors will need to be very good doctors indeed"[1]

The Widdicombe File

XLVI MERIT AND MONEY

MY DEAR WHIDDON,

WHILE you and the others were talking of Merit Awards, I having neither merit nor expectations let my thoughts stray to the size of my electricity bill and how to fish the Herring-guts pool in high water But what I overheard of your conversation returned to me on the way home, and I am bound to say that all of you were barking up the wrong tree

There is a sum of money put aside to reward merit among the consultants So long as you accept this idea (and would not prefer the fund to be used to reduce the National Debt) the argument is limited to the way in which it should be distributed If you are an egalitarian you will say that merit is indivisible and that everyone should get an equal cut of the cake—like Prime Ministers or postmen Alas for the vanities of this sordid world, but some of our colleagues are convinced that they have more than their share of merit and are quite agreeable to some financial recognition of their superior talents Mere titles of honour—like the F R C P or Hero of the World Medical Struggle against Scabies—are not enough How then shall we select the meritorious?

Length of service alone has, I believe, some advocates, and, seeing that a grey head is reassuring, there is a lot to be said for it provided that we forget the word "merit" It would remove every imputation of favouritism, prejudice, and fancy and might dissuade those, deepest in the red from migration to Botany Bay Or the consultants might be paid "by degrees" For example, if a D L O or D C H is valued at £*x* per annum, then an M D would be worth £2*x*, and the F R C S £3*x* an F.R S would be worth at least £5*x*, honorary degrees score double, and a Nobel prize would give game, set, and match This scheme would improve the finances of the examining bodies, but I foresee one or two—perhaps minor—disadvantages A third alternative is to estimate worth by its contributions to original knowledge, but then, I fear, the glittering prizes would fall not to sharp swords (or scalpels) but to chest physicians or even biochemists

I thought I knew the evils of the present system of selection, but, to judge from what I overheard, simony and nepotism are the least of the crimes committed by the selectors, who are, moreover, so deranged as to be unfit to judge the class for stump-rooted carrots at our flower show Maybe this is all true, but I have a suspicion that what worries your colleagues is that (*a*) they have no award, (*b*) they do not know how or why A N Other got his award, (*c*) it would be nice to know if they would get an award later I sympathise with you on every score, but so long as the distribution of these gilded baubles depends upon intangible—perhaps indiscernible—merit, so long will 60% of consultants tell us that the cards were stacked before the game began

I have no doubt that we must start again Who are those doctors whom we all hold in the highest honour? Of this there is no doubt They are those—not of necessity those with most degrees or the largest practices or the most clubbable—whom we others, as husbands and fathers, summon to the bedside of our ailing wives and children This has always seemed to me the highest honour which any doctor can pay to another, and the Georgian cream-jug (or the dozen of champagne) is but a poor token of our trust and gratitude It is these Physicians and Surgeons in Ordinary to their unhappy colleagues who deserve all the rewards for merit which are available, and I suggest that the fee for a domiciliary visit to a doctor's family should be a thumping one—say 50 or 100 guineas or whatever figure the fund will allow The cream-jug will give some permanence to a reward which, thanks to the Commissioners of Inland Revenue, will be rather evanescent

It will be hard on the venereologists? Well, the present scheme has not pleased everyone

Yours sincerely,
Harry Hawke

Public Health

Occupation and Mental Illness

In a Supplement on Mental Health,[1] the Registrar General relates mental illness to occupation Admissions to mental hospitals in 1952 and 1953 are analysed to show the diagnosis on admission and the social class of the patient (I professional, II managerial, III skilled, IV semi-skilled, V unskilled) In addition, first admissions of men aged 20 and over in the five years 1949–53 have been specially analysed in three groups of diagnoses and a hundred occupation groups

Among males aged 20 and over, admission-rates in 1953 for schizophrenia, manic-depressive reaction, and psychoneuroses were all highest for patients in occupations assigned to social class V For disorders of behaviour, character, and intelligence classes I and V had rates considerably higher than the other classes Estimated first-admission rates for schizophrenia increased from 88 per million population in class I to 383 in class V, for manic-depressive reaction rates were 235 in class I and 213 in class II, increasing to 392 in class V Analysis within the classes suggests that certain occupational groups are associated with first-admission rates above the average, but such association is less clear in manic-depressive reaction than in schizophrenia In general

"Adverse rates appear to be connected with a high standard of education, with clerical work, domestic work, branches of the catering industry and with labouring Why this should be so is open to speculation and it is difficult to separate cause and effect

"How far the actual work and how far the general living conditions which certain types of industry involve are connected with mental health is uncertain Detailed ecological studies are required, taking in the worker's whole environment, and a start might possibly be made among those groups which have been shown to have exceptionally high or low admission rates"

Smallpox

A 53-year-old man died of smallpox in New Ferry Isolation Hospital on May 20 He was the man mentioned in our note last week (p 1135) His wife's illness has been mild Up to Tuesday of this week no further cases had been reported, and it is hoped that the outbreak may have been curtailed

In England Now

A Running Commentary by Peripatetic Correspondents

The Siamese cat was, I thought, a brilliant piece of therapy—much better than the hemicolectomy I had undertaken for the removal of Mrs A's cæcal growth, which her Alsatian had brought to our attention Mrs A, in her late 60s, lived alone but for the Alsatian whom she adored, in fact affection started the sequence of events, for the dog jumped up to greet her and the blow of his paws upon her abdomen suddenly caused her to feel faint She lay down, and a contrite dog, sensing something amiss and anxious to make amends, went to lick his mistress's face, once more his weight fell upon her abdomen Mrs A came into hospital and her neighbour ordered the dog to be shot

The almoner looked at me askance must it be a Siamese, wouldn't any cat do? I explained the particular merit of a Siamese, that it more than any other cat would recognise one person only as its mistress, would love its mistress and her alone, and would cause no accidents by boisterousness The almoner grasped the idea and in no time, so it seemed, had succeeded, so Mrs A was able to return home with a companion My brainwave exceeded my best hopes The singleness of that cat's affections would have done credit to Penelope, Mrs A was always greeted with a furry rub across her legs not so her visitors At the sound of approaching footsteps that cat would leap to the top of a cupboard in the hall and then pounce with full fury on an unsuspecting head It had extraordinary virility, being unable to come to grips with the inmates of a neighbour's aviary it sat outside the wire and gazed with such malignant intent that one by one the priceless birds fell with terror to the ground After six had died their owner registered a strong complaint, but on hearing how Mrs A came by her cat was filled with remorse, and the ensuing friendship between Mrs A and her neighbour must really be put to the cat's credit

There's no doubt that the idea was a masterstroke (and I recall with pride and pleasure how I used to draw the attention of the students to this, the most important part of the patient's treatment) But I am growing a little uneasy Mrs A now has hepatic metastases and must soon be admitted to a home Who will look after the cat?

* * *

I was just about to give the injection for the I V P when I noticed that the iodine skin test which the patient had been asked to apply the previous afternoon looked peculiarly yellow The simple instructions delivered with the iodine ampoule had perhaps not been simple enough, and the patient had taken the ampoule, if not the instructions, untouched to his family doctor The doctor advised him never to use iodine as it produced such reactions, and painted the forearm with acriflavine

* * *

Our senior partner took a Bentley into partnership long before such a desirable symbiosis became an advertising gimmick General practice must have been a most rewarding experience in those far-off happy times No shouting over the rhonchi, no flutter of hire-purchase deeds, none of the contorted humiliation of the new poor as we squeeze into our little pressed-steel boxes While the expense accounts and industrial assets glide by, we sigh for the golden years All but the senior partner He refuses to sigh for anyone The Bentley's coachwork, like his own, may look a bit battered, and her lines betray the years But her works, like his own, are as big-hearted as ever You might be tempted to think that they are dead but they won't lie down Not a bit of it Neither of them is ready for the scrapyard yet They've done a mere fifty thousand since they each had a rebore Just fill them up, point them in the right direction, and watch for the cloud of dust Proud they are of their vintage maybe a little too proud That was their undoing The old boy wanted a few days' fishing in Scotland, so my wife and I went with him, a gaff and a catheter in the boot All went well until we were dawdling at 55 over the Rannoch Moor then a Jaguar had the nerve to overtake

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[1] The Registrar General's Statistical Review of England and Wales for the two years 1952–53 supplement on Mental Health H M Stationery Office Pp 208 1958 11s 6d

The senior partner's hackles rose up. A nicely polished brogue shot down. My wife gripped the edge of her seat. I felt the kick of adrenaline. The Bent roared with delight down the narrow road, over the concrete bridge, and took the Jag offguard on a sweeping curve. The old boy's triumphant blast on the horn was more expressive than any manual gesture a lesser mortal might have been tempted to make through the rear window. But the effect was precisely the same. The Jaguar opened up and sat tight on our tail. Glencoe came in sight. I thought of the massacre. Ballachulish ferry seemed so far and yet so near as time and the heather flashed by. The Jag was pressing us hard as we thundered down the glen. The old man was pressing the Bentley, and just about holding his own, when centrifugal force took over from gravity. The road swung away to starboard, and we were airborne. The senior partner's remarks were irreverently unsuitable for our flight. However, the Scottish bogs are resilient, and never perturbed to absorb a couple of tons of kinetic energy. We made a rather spectacular belly-landing, and that was that. By the time I had helped out the missus, old King Lear was striding over the blasted heath shaking his fist at the back of the Jaguar. His rivals were far more in need of shock treatment than he was. He saw the point, and came stumping back to the car. Old faithful never let him down. There in the cubbyhole was an intact bottle of Scotland's best. It was a jolly party that zig-zagged into Fort William. The partnership was unbroken. Someday we look like having a Bent of our own. My wife is the old boy's daughter.

* * *

The chief was doing his round one morning with the registrar, houseman, and firm in attendance when he came to a patient who was suffering from chronic nephritis. Picking up the chart at the bottom of the bed he noticed that for day after day the urine had been marked up "N.A.D." Turning to the clerk in charge of the case he said "I see that you're very keen, my boy, and have obviously been testing the urine every day. Tell me, what was the albumin content?" The clerk replied "I don't know, sir." On being asked whether there was any blood present he once more replied "I don't know, sir." This rather upset the chief, who once more looked at the chart, and, seeing column upon column of N.A.D.s, asked "Well, my boy, what *do* you mean by writing N.A.D.?" "Not a drop, sir."

* * *

The rugger type who nearly knocked over your peripatetic correspondent on the Holborn escalator last week is a pleasant soul, but an unpunctual one. He is often in a hurry. Having boxed a good deal, as well as playing rugby, his features appear hostile even when he is at his most amiable. While hurrying down the escalator he recognised instantly that the man he bumped was a psychiatrist. He also perceived that any action other than a hasty apology over his shoulder would lead to ten minutes' discussion on underground neurosis. This would have made him even later than he was already.

Many of us are prone to projection, and perhaps it is a conspicuous symptom in rush-hour psychopathology.

* * *

The patient from Chipping Sodbury had his cycle clips on. I saw on his treatment card that he had been performing on the static bicycle for the benefit of his knee and remarked that there was nothing like taking his exercises seriously. He blushed and apologised for not taking off the clips before he came in, but as he was a little late for his appointment he had come straight in and had not even had time to park his bike.

As I saw him later, starting on his long ride home, my mind went back a few years and many thousand miles to Mauritius, where I had once watched a group of women and children huddling under the wall outside the door of the X-ray department, seeking the little strip of shade that the eaves made in the high summer sunshine. Soon their turn would come to escape from the blistering midday glare into the cool interior for their general ultraviolet-light treatment.

Letters to the Editor

IODINE PROPHYLAXIS OF GOITRE

SIR,—In your issue of May 17 Dr. Greenwald criticises the proposal to iodise salt—on two grounds. First, that goitre in many parts of the world is diminishing in prevalence, and, secondly, that iodised salt is not without its possible dangers, supporting his thesis with 20 references to the literature dating from 1885.

The literature on goitre is so vast and often so conflicting that support can be found for almost any theory. Thus, as regards the evidence of recruits rejected because of goitre for military service in Switzerland, Eggenberger[1] declared at the Third International Conference that in the Swiss county of Appenzell the introduction of iodised salt was accompanied by a decrease in the incidence of goitre in recruits *from 7% to 0.1% in 16 years*. *More recently* Nicod[2] at *the* 1953 W.H.O. Conference on endemic goitre stated "Un seul canton reste refractaire a l'usage du sel iode, c'est celui d'Argovie et, fait interessant, c'est celui qui aujourd'hui reforme encore le plus de jeunes gens pour goitre." A comprehensive review of no less than 939 articles in the literature published this month provides much further information.[3]

The second contention can be answered more concisely. There is no accredited record of hyperthyroidism arising from the prophylactic use of iodised salt. There *are* reports of its occurrence following pharmacological doses of iodine, the so-called Jod-Basedow.[4]

However, Dr. Greenwald's scholarly researches are of more than historical value: they do help to show that the distribution of simple goitre may be related to the geography, geology, and dietary habits of a country. When the overall intake of iodine is low, the incidence of thyroid enlargement may well be determined by goitrogens which do not normally affect us, such as calcium.[5]

Dr. Greenwald's intransigence in opposing iodised salt can perhaps best be countered by the statement of an equally staunch supporter of iodine prophylaxis, Dr. Kimball.[6]

> "We have definitely proven that:
>
> "(1) Simple or endemic goitre is a deficiency disease and this deficiency is iodine in our food and drink. This iodine deficiency was caused primarily by geological conditions and has been made worse by our refinement of foods such as salt.
>
> "(2) The addition of an exceedingly small amount of iodine to our food in endemic goitre regions prevents goitre. The most practical method yet devised is iodised salt."

London, S.W.15. SELWYN TAYLOR.

THE FUTURE OF THE PUBLIC HEALTH LABORATORY SERVICE

SIR,—Your entertaining correspondence on this subject has not proved as stimulating as I had hoped, and the criticisms of pathologists-in-charge made by "London Bacteriologist" (April 26) and "Hospital Bacteriologist" (May 10) have fallen rather flat.

As a pathologist-in-charge whose entire bacteriology department is run by the Public Health Laboratory, I can assure all your correspondents that, with a little good will, cooperation on both sides, and a sense of humour, the system works excellently, and, what is important, to the satisfaction of my clinical colleagues.

Hospital Bacteriologist will no doubt be delighted to know that I would not dare, even if I so wished, to "inter-

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1. Eggenberger, H., Messerli, F. M. Transactions of the 3rd International Goitre Conference; pp. 64-67. Washington, 1938.
2. Nicod, J. L. *Bull. Wld Hlth Org.* 1953, 8, 259.
3. Kelly, F. C., Snedden, W. W. *Ibid.* 1958, 18, 5.
4. Stanbury, J. B., et al. Endemic Goitre: Adaptation of Man to Iodine Deficiency. Cambridge, Mass. 1954.
5. Taylor, S. *J. clin. Endocrinol.* 1954, 14, 1412.
6. Kimball, O. P. *Transactions of the 3rd International Goitre Conference*, pp. 57-63. Washington, 1938.

fere" with colleagues bearing the imposing titles of Director and Deputy Director, whilst London Bacteriologist may well remind himself, in his anxiety over the absence of bacteriological advertising matter, that, while appointments are still made to hospital laboratories by advertisement, short list, and interview at which representatives of the candidates' prospective colleagues are present, our Public Health friends are thrust upon us by edict from London

Downtrodden as I may appear, however, I remain sufficiently master of my soul to disclaim anonymity

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A J N WARRACK

TOTAL GASTRECTOMY FOR BENIGN PEPTIC ULCER

SIR,—I wish to comment on the conclusion drawn by Dr Balint and Mr Gummer in their paper of May 17

The statement that the operation of total gastrectomy "is justified in patients with obstinate anastomotic ulceration not arrested by adequate gastrectomy and vagotomy" requires modification Until recently "adequate vagotomy" implied only an ill-defined impression at the time of operation A test for completeness of vagal-nerve section at the time of operation has recently been described by Burge and Vane[1] Their experience with this test must raise doubts about any conclusions based on operative assessment of complete vagotomy

It would seem, therefore, that before the operation of total gastrectomy can be considered justified or advocated for adoption in the treatment of "pernicious ulcerators",[2] some method of testing for complete vagal-nerve section must be employed

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CHARLES G CLARK

SYMPTOMS AFTER CHOLECYSTECTOMY

SIR,—May we reply briefly to certain points raised by Mr Dudfield Rose (May 17) in his criticism of our article of May 3?

We failed to find any evidence of biliary dyskinesia in the series of patients we examined at periods of 1 to 7 years after cholecystectomy Mr Dudfield Rose suggests that our conclusions in this respect are unwarranted unless we carried out one or more of the following investigations serial cholecystography, per-operative manometry, and chronovolumetric estimation of bile Serial cholecystography was not part of the preoperative investigation in this series We believe the radiation exposure involved is unjustified Furthermore, the method requires visualisation of the gallbladder at cholecystography, so would have failed in 45% of our cases Much has been written on per-operative manometry, but we are not convinced that valid records of biliary pressure can be obtained in man under anæsthesia, even if premedication is omitted The third method, chronovolumetric estimation of bile, is admitted by Mr Dudfield Rose to be sometimes misleading

We found that only 7 patients (5%) had symptoms between operation and follow-up examination referable to the biliary tract All had organic lesions which adequately explained the symptoms stenosis of the sphincter of Oddi, pancreatitis, stone in the common bile-duct, and postoperative adhesions

All other patients with postcholecystectomy symptoms had extrabiliary lesions which we considered as the cause In view of the necessarily brief data we gave, we are surprised that Mr Dudfield Rose has been able to postulate that certain of these cases had hypotonic dyskinesia The following details of two of the cases cited by him are typical of all cases in this group, in that the symptoms do not originate in an autonomic imbalance in the biliary tract

Case 8—This woman has been completely relieved of her preoperative biliary pain and flatulent dyspepsia she now presents with lower abdominal discomfort and constipation A clinical suspicion of diverticulitis has been confirmed by barium-enema examination

Case 10—This woman has been similarly relieved of preoperative biliary pain and dyspepsia *her present symptoms are of classical* migraine with hemicrania followed by bilious vomiting, occurring at the time of menstruation

In both cases intravenous cholangiography has demonstrated a normal biliary tree

Department of Surgery,
Western Infirmary,
Glasgow

W BURNETT
R SHIELDS

TREATMENT OF BREAST CANCER

SIR,—The paper from the Mayo Clinic[1] and your leading article of Feb 1 refer to a matter of great importance, and, coming from such sources, their conclusions must carry considerable weight

Several of your correspondents have already commented on the statistical aspects of the Mayo Clinic report, but some of the clinical implications should also be noted

McWhirter,[2] in the paper from which the Mayo Clinic workers take his survival figures to compare with theirs, clearly defines the "operable group" (for the radical operation) and confines his use of the term to the Manchester clinical stages I and II, excluding (*a*) all cases of locally advanced disease (i e, all cases showing "complete fixation of the primary tumour to the pectoral fascia or to the ribs, fixed nodes in the axilla, enlarged supraclavicular glands, or widespread involvement of the cutaneous lymphatics over the breast") and (*b*) those with distant metastases With this definition, I feel sure, the great majority of surgeons who practise the radical operation would agree, indeed some would define the operable group even more strictly

Unfortunately, as clinical staging of breast cancer is not used in the Mayo Clinic, accurate direct comparison of the two series is not possible However, unless the criteria of operability (for the radical operation) at the Mayo Clinic differ very considerably from those elsewhere, one must assume that their "operable" cases in the period 1941–47 consisted almost if not entirely of cases in stages I and II Crile[3] has already pointed out the similarity of the five-year-survival figures from the two centres on the basis of this assumption

On the other hand, if this assumption is incorrect, the Mayo Clinic series may contain a considerable number of cases of locally advanced disease (as defined above) If this is so, the five-year-survival *rate which is reported* suggests that the radical operation is being restricted too severely in other centres, and all surgeons dealing with mammary cancer will need to reconsider their criteria of operability In view of accumulated experience of the survival figures in such cases elsewhere, they are unlikely to do this unless the Mayo Clinic workers can produce figures giving the numbers of cases in the "operable" and the "locally advanced" groups (as defined above) in their series, with the corresponding survival-rates for each group

It is evident that until an international system of clinical staging is agreed upon and put into effect no accurate comparison between survival-rates at different centres can be made, and consequently the comparative value of different forms of treatment cannot be assessed It is for this reason particularly that the meeting of the International Cancer Congress in London in July, at which this matter is to be considered, is of such importance

Proceeding one step further, it would seem that the pathological grading of mammary cancer may well be of

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[1] Burge, H , Vane, J R *Brit med J* 1958, i, 615
[2] Balint A , J , Cooper, G W , Price, E C V , Pulvertaft, C N , Swynnerton, F B A *Lancet*, 1957, ii, 551

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[1] Berkson, J , Harrington, S W , Clagett, O T , Kirklin, J W , Dockerty, M B , McDonald, J R *Proc Mayo Clin* 1957, 32, 645
[2] McWhirter, R *Brit J Radiol* 1955, 28, 128
[3] Crile, G , Jr *Lancet*, 1958, i, 739

prime importance Geographical differences in the proportions of tumours of high and low malignancy could do much to explain variations in survival figures

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IAN MACKENZIE.

TREATMENT OF OBESITY

SIR,—The letters by Dr Mullins (April 5) and Dr Badham (April 20) on the treatment of obesity completely ignore the psychosomatic aspects of the overweight patient.

It is easy to put a patient on a diet, give appetite-reducing pills, and get a considerable reduction in weight However, this weight is regained almost invariably once supervision is discontinued While treatment appears to have been a success, long-term follow-up reveals failure of such a therapeutic regimen The reason for this is that increased appetite is considered to be the basic cause of overweight, whereas in fact it is only a symptom of a particular patient's reaction to underlying psychological stress

Patients who overeat do so because of unsatisfied oral needs When they are unable to face their problems on an adult level they regress to the level of infancy Just as a baby turns to the breast for comfort when he is unhappy, so do obese people overeat during periods of stress Other manifestations of this regression to the oral phase are excessive smoking during periods of difficulty, nail-biting, and the chewing of gum and tobacco

Obese patients require psychotherapy, which should be devoted to helping them to express themselves and "getting off their chests" those things which are distressing them If this is done they will no longer find it necessary to regress and consequently to overeat

Central Islip State Hospital,
New York.

M G JACOBY.

TREATMENT OF ASTHMA AND HAYFEVER BY HYPNOSIS

SIR,—This correspondence is of great interest to those who work in the field of hypnosis

Some allergists hold that the allergic reaction is the only stimulus responsible for asthma, while others say that allergic disposition may be present in a patient but under normal conditions the allergy may be latent or mild and yield to conventional treatment. Under the stress of emotions, however, it can become chronic and disabling When this occurs it can again be eliminated by therapy of the emotional factors even though the skin-sensitivity tests remain the same

Herxheimer's experiments[1] with house dust showed that among the patients giving a positive skin reaction a high proportion did not give any bronchial reaction Conversely, some patients' skin reaction was negative but they had bronchial spasms In 1954 he again stated[2] "we have tested the skin responses of 300 patients with respiratory allergy and of 100 normal subjects, and have found their outcome in the same subject most variable Only in three out of 21 patients could we reproduce exactly the same result on two different occasions"

Bignall[3] says "Skin testing seldom aids in diagnosis and treatment It is generally more profitable to explore the patient's mind and his environment than the lungs, sinuses or hypersensitivity reactions

Since we take care of people and not just their diseases we cannot help dealing with their emotions The more knowledge the doctor possesses of the emotional factors in his patient's illness, the more capable will he be in dealing with him and his disease In the asthmatic, alteration of the psyche is the rule rather than the exception One physician quotes the case of a patient who is sensitive to ragweed pollen, but who, interestingly enough, does *not* have these attacks when his mother-in-law is out of town.

With my own asthmatic patients, Sally and Victor were sensitive to feathers Robert was sensitive not only to feathers but also to cats and birds Barbara was sensitive to chocolates while Brian could not tolerate onions or plums Mrs C could not eat pork, cheese, or eggs, while Theo could not stand dogs Tim was upset by dust and also got tight and wheezy when the weather was dull and damp (how do you skin-test for that?) Mrs B hates gas and smoke, so does Mrs P who works in a pub Mrs B cannot eat fish, potatoes, or milk pudding, while Mrs D cannot face milk, fish, cheese, or eggs

With repeated reassurance under hypnosis all these patients have become immune to their so-called asthma-producing allergies

London, W 1

A P MAGONET

CARDIAC SYNCOPE AFTER SWALLOWING

SIR,—In his report of a patient with cardiac syncope induced by swallowing, Dr James (April 12) has given a rather complete explanation of some of the factors that may have been responsible

He and your readers will find it of interest to review the case described[1] by Dr S Glatzer, of Brooklyn The patient, following digitalisation, began to experience syncope immediately after swallowing water It was demonstrated that carotid-sinus pressure induced a typical syncope Two days after the digitalis had been discontinued, neither deglutition nor carotid pressure could cause syncope

Dr Glatzer felt that the sequence of events in this patient could be attributed to increased sensitivity of the carotid sinus, accompanying digitalis toxicity He also pointed out that increased carotid-sinus sensitivity occurs in myocardial infarction

Thus, in Dr James' patient, the digitalis and the infarction were undoubtedly ætiological factors, and so possibly was the midœsophageal diverticulum, with the carotid sinus acting as mediator for the sensitising influences

Seaside Memorial Hospital,
Long Beach, California

GEORGE X. TRIMBLE

ALPHA TOCOPHEROL AND CONGENITAL ANOMALIES

SIR,—Mr E V Shute[2] claims to have demonstrated that the administration of alpha tocopherol to potential fathers prior to conception, in cases where a previous child with an anomaly had already been born, was effective in preventing further malformations If this were in fact the case, the study would be of very great importance It is unfortunate therefore that Mr Shute's conclusions are open to criticism

He concluded, on the basis of his previous experience, that the risk of a subsequent abnormal child, by his definition, in a family where one has already been born, is 1 in 7 In his experiment he gave alpha tocopherol to 17 such fathers prior to conception The 17 conceptions resulted in 15 normal children and 2 "anomalous infants" Professor Randal Cole concluded that the chance of getting 15 normals out of 17 in these families with an abnormal child was 1 in 500 This result was obtained, however, by reckoning in the index cases or propositi, who had drawn attention to the families in the first instance This is inadmissible. Mr Shute's own method is the correct one (reckoning the probability by taking account of all the siblings except the index cases) and his experience showed this to be 1 abnormal in 7 sibs, which conforms as nearly as possible to the findings in the cases where alpha tocopherol was given to the fathers

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[1] Herxheimer, H *Int Arch Allergy*, 1951 2 40
[2] Herxheimer H McInroy P Sutton K. H., Hudson H L. Hudson, H M D *Brit med J* 1954 i 1379
[3] Bignall J R. *Med Pr* 1953 230, 526

[1] *Circulation* 1957, 16 107
[2] Shute E. V *J Obstet Gynæc Brit Emp* 1957 64, 390

In other words, there is no evidence in these findings that the alpha tocopherol had any effect on the outcome of the pregnancies

Fountain Hospital,
London, S W 17

BRIAN H KIRMAN

GONADAL DYSGENESIS

SIR,—Dr Hubble (May 10) suggests that Lawson Wilkins' textbook[1] contains what is already an adequate account of the subject of the primary testicular disorders of the Klinefelter group I am sure Dr Wilkins would be the last person to make this claim on his own behalf (see his textbook, particularly the second paragraph on Primary Testicular Disorders, p 236, and the footnote on p 232) Knowledge in this field is advancing exceedingly rapidly In my own paper in your issue of May 3 I was concerned chiefly to present facts for instance, to describe testicular appearances in this condition before puberty, for remarkably little is known about these early cases, the analysis of the significance of these facts was necessarily brief The views of the Glasgow group interested in this subject, to which I belong, have been stated more fully elsewhere,[2] and will I hope clear up some of Dr Hubble's doubts

It is generally agreed by those working in this field that the whole subject of the nomenclature of testicular disorders in particular, and abnormalities of sexual development in general, needs a thorough overhaul, and I believe there is some hope of an international committee being set up in the near future to attack this problem

Western Infirmary,
Glasgow

M A FERGUSON-SMITH

TETANUS AND IMMUNISATION POLICIES

SIR,—No-one would deny that it is ideal for children to be actively immunised against tetanus, not only to protect against tetanus but also to avert the danger of anaphylactic reactions due to A T S in the increasingly large proportion of the population who have received this injection

But it seems scarcely worth providing active immunisation against tetanus unless there is some way of telling in the future which child has, and which has not, been immunised Obviously, the easiest way is to tattoo in large letters on the child's body " Immunised against tetanus give booster, not A T S ", but this and any other tattooing policy is not going to be accepted by our patients—and who can blame them? Nor can identity discs, or cards to be carried in purse or wallet, be the answer They will be lost or left at home when most needed Nor is it any good relying on the patient's medical record card, even if every immunisation is conscientiously entered (and the vast majority are not) the record cards are available only at the doctor's surgery Ask the parents? I would estimate that half of them do not know for certain the diseases against which their children have been protected

What is the answer? It seems to me that the *only* possible answer is to have a national policy for immunisation In January my colleagues and I wrote a letter[3] drawing attention to the veritable state of confusion that exists over the whole policy of immunisation and put in a plea for a national policy The decision whether or not to immunise against tetanus, and if so whether to use single or combined vaccines, varies from one doctor to another, from one clinic to another, and from one county to another in a completely haphazard manner We must be free to treat and prescribe for our patients according to our own lights, but this excess of individuality is of benefit to no-one A national policy for immunisation would have to be worked out by some advisory body (for example, an M R C committee), but the addition of poliomyelitis to the already formidable list of routine immunisation procedures makes this a matter of urgency, A plan, as simple as possible and including tetanus toxoid, is needed, and the argument in favour of combined vaccines seems overwhelmingly strong

The only possible objection to a uniform national plan of immunisation is a national dislike of uniformity I confess to at least my fair share of this dislike, but in this particular instance it would seem a trivial objection against the urgent necessity for such a plan

Wantage,
Berks

I S L LOUDON

RECORDS OF IMMUNISATION

SIR,—We agree wholeheartedly with Dr Randall (May 3) that something could be done to issue permanent records to those people who have been or are being actively immunised

Here all casualties are actively immunised against tetanus, commencing six weeks after their injection of antitoxin or at once if they react to an intradermal test dose The course was originally aimed specially at agricultural and slaughter house workers, and allergic persons, but is now available to everyone

Cards have been printed specially to record these injections (thick yellow cards for the patient, and thinner white ones for filing) and an appointment system is used So far only about 5% of patients who have commenced the immunisation course are having to be sent for a second time and about 10% of those just commencing The proportion of patients who do not remember to bring their yellow cards with them at subsequent injections is even smaller

By having these standardised cards the course is open to anyone in the district who desires it, and the cooperation of the various works' doctors, general practitioners and the medical officers of health is being obtained, so that if any of them wish to immunise their patients they may do so, and after they notify us, we forward the patients' cards and add their names, &c , to our own records

Casualty Department,

P A GARDNER

Pharmacy Department,
North Lonsdale Hospital,
Barrow-in-Furness

A K McIVER

SIR,—I read with great interest the letter from Dr Thomas Scott (your issue of May 17) on the use of toxoid and A T S I think the points he makes should be emphasised up and down the country I think, however, it should be made clear to Dr Scott that it is extremely difficult in a busy casualty department for anyone to find out if patients have previously been immunised by means of toxoid

In the nine years since I took charge of this department not a single patient has ever volunteered that they have been immunised against tetanus I make a practice of inquiring from ex-Service candidates whether they have knowledge of immunisation against tetanus It is rare to get any satisfactory answer

I would suggest that in every case where immunisation has been carried out against tetanus, a suitable card should be provided for the patient in which it states unequivocally that this has been carried out The responsibility for providing

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1 Wilkins, L Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence Springfield Ill, 1957

2 Ferguson-Smith, M A , Lennox, B , Stewart, J S S , Mack, W S Proceedings of a Symposium on Sexual Differentiation and Development 1958 (In the press)

3 Loudon, I S L , Seward, C W , Hawkey, J K *Brit med J* Jan 4, 1958, 39

the card should fall (*a*) on welfare clinics where the triple vaccine is used, (*b*) school medical officers, and (*c*) medical officers in the Forces

United Leeds Hospitals
MAURICE ELLIS

SIR,—As a casualty officer seeing many cases of injury I was interested in Dr Scott's letter

It is our experience here that a large number of patients who attend are able to tell us that they have been treated elsewhere for injuries and have been given injections, but they have no idea what they were given or why, and in many cases they are extremely vague about the time of the injury

It has been our custom for some time past to issue all patients in need of toxoid with a record card, on which is entered the amount of the toxoid given, the date on which it was given, and a reminder date for the reinforcing dose This card, which is of pocket size, is given to the patient with instructions that it should always be carried with him and produced whenever he has to be given any injection The amount of clerical work in filling in these cards has been found to be negligible

The card, which is obtainable from Messrs Burroughs Wellcome, contains space for the recording of any type of protective inoculation, with a small space for the blood-group In our experience the patients are pleased to receive these cards and do appreciate that it is in their interests that they carry them with them, and we have no difficulty in getting them to report on the appropriate date for their booster doses of toxoid

Solihull Hospital
H WYNFORD JONES

YOUNG GIRL, OLD GIRL?

SIR,—In a review in your issue of May 17 you speak of a young girl of nineteen, making use of what is now accepted terminology According to this system of classification, a girl is unequivocally juvenile, but a young girl is someone considerably older who might almost be described as a young woman, were that permissible It seems, however, that agreement is still lacking on the gradations that may correctly be used to bridge the gap between this phase and that later period when the young girl has finally acquired the status of an old girl

Bushey Heath,
Hertfordshire.
F CAMPBELL ROSE

ORAL TREATMENT OF PERNICIOUS ANÆMIA

SIR,—We are grateful for the comments on our article on pernicious anæmia by Dr Latner (May 17, p 1077), who has worked for so long in this field with such distinction. We feel, however, that to criticise the dose given in the first week and yet ignore the lengthy maintenance period on low dosage is somewhat eccentric We were quite aware that daily oral doses of 100 µg of vitamin B_{12}, no matter in what form it was given, would produce a response of some kind We were less interested in this initial response than in ascertaining whether the vitamin-B_{12}-peptide could maintain patients in full health over long periods on small doses We believe that the literature is already overcrowded with reports of short-term responses to various preparations and we had no desire to confuse the picture still further

Although it is true that responses can be obtained with 5 µg of vitamin B_{12}, the massive doses of “ intrinsic factor ” required to facilitate its absorption (one thousand to two hundred thousand times the amount of vitamin) indicate that such preparations are not really very effective on a weight basis We have not attempted, as yet, to determine the minimal effective daily dose of our preparation in terms of vitamin B_{12}, but no matter what this is finally discovered to be, as it is complexed with less than seven times its weight of peptide, it remains quite easily the most effective preparation for the oral therapy of pernicious anæmia yet described

Lastly we do not deny that there is some factor within the normal stomach which brings about the relevant proteolysis—indeed, that is precisely what we have already said in our article That, however, is totally different from believing in the existence of the “ intrinsic factor ”, as currently understood, which is supposed to combine with pure vitamin B_{12} to facilitate its absorption

St. Helens Hospital
J G HEATHCOTE
F S MOONEY

“ THESE DYING DISEASES ”

SIR,—Dr Vickers states in his letter of April 19 that “ cases of non-specific urethritis are now the major problem, and these are in need of general medical investigation and care ” If the V D service is disbanded, as he suggests, who will diagnose these cases from gonorrhœa and study the relation of promiscuous exposure to certain cases of urethritis? Who will investigate the various types of non-specific urethritis and study the relationship of urethritis and prostatic infection to rheumatoid arthritis and other rheumatic conditions I believe that the great majority of physicians, surgeons, and general practitioners are glad of the specialised help that venereologists can give in trying to solve these problems

In many of the large cities gonorrhœa itself is a major problem and the ultimate success of modern methods of treatment is by no means assured Contact tracing and follow-up of defaulters, therefore, remain essential to control the disease, and this would become impossible if the cases were scattered among practitioners

The V D departments have an important part to play in investigation of doubtful blood reactions in pregnancy In the genuine cases of syphilis, treatment and follow-up of mother and baby can best be done through an organised V D service The immigration from countries with a high rate of syphilitic infection makes this a formidable task in some areas

If, as Dr Vickers states, the majority of cases of late syphilis are treated by the physician specialising in the organ mainly affected, and not by a venereologist, then the incidence of late syphilis in this country must indeed be high and cause for grave national concern

One important problem is not dealt with either in Mr King's original article (March 29) or in subsequent letters This is the small-town clinic where in many instances the number of patients attending does not justify the expenditure on staff, buildings, and equipment Many of the patients in these areas travel to the nearest large centre where there is less chance of casual recognition There is no easy solution to this problem, and I think each individual clinic needs careful consideration to decide whether (*a*) better facilities would improve the attendance or (*b*) the clinic should close

The General Hospital,
Birmingham
G H KNIGHT

SIR,—The letter by Dr Willcox (May 24) about the increasing incidence of gonorrhœa in spite of antibiotic treatment recalls a conversation which I had with Sir Alexander Fleming a few weeks before his death

He told me that he thought the antibiotic era, especially in relation to venereal infections, would be over in about five years I replied that although he was more able to judge than anyone else, surely he underrated the value of penicillin

The alarming statistics of the increase of these "dying diseases" suggest that Fleming's statement was justified

London, W 1 T Anwyl-Davies

A LOW-RESISTANCE RESPIRATORY VALVE

Sir,—We are grateful to Dr Cunningham (April 5) for pointing out that our brief report (Feb 22) on a low-resistance valve gives the false impression that the valve of Bannister and Cormack is not of similar low resistance This was not intended Of the many valves examined, a few were included in our report, and two only were discussed—the valve of McKerrow and Otis, which has a large deadspace, and that of Bannister and Cormack The latter has hinged valve flaps operated by gravity, and although we regret that we have not had one of their valves to test, it seems unlikely that it could operate effectively during tests of maximum breathing capacity where respiratory rate may exceed 200 per minute

Pneumoconiosis Research Laboratory,
Braamfontein, Johannesburg S Zwi

CHANGES IN THE LIVER IN GLOMERULONEPHRITIS WITH ŒDEMA

Sir,—There is no doubt that the combination of renal and hepatic disease is not a coincidence, since both organs have excretory functions and may be damaged by the same toxic and infective agents, as in yellow fever and Weil's disease Practically all the studies published deal with the effect of liver disease on the kidneys

Boyd[1] could find no changes in liver-function tests in cases of nephritis We studied 51 patients with œdema—caused by acute glomerulonephritis in 13, subacute nephritis in 9, subchronic nephritis in 23, cardiac failure in 3, and malnutrition in 3 They were investigated by means of several liver-function tests, and repeated liver biopsies stained and examined for structure, protein, glycogen, and fat content

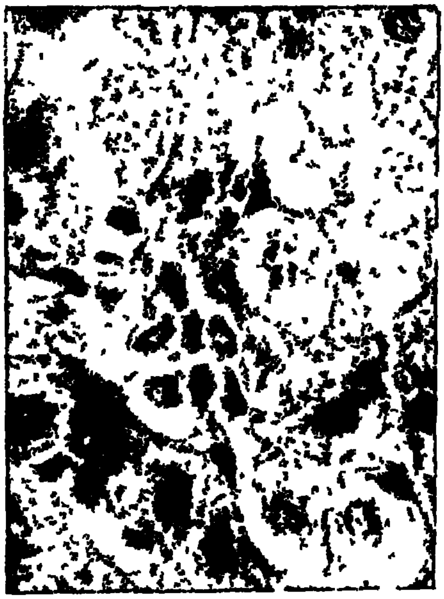

Fig 1—In the centre is a minute focus made of one or two disintegrating liver cells infiltrated by neutrophils (×450)

To summarise the results in the 45 cases of nephritis

1 *Clinical*—The liver was found to be progressively enlarging in proportion to the duration of the œdema in 40% of the cases of glomerulonephritis

2 *Liver-function Tests*—The galactose-tolerance test was disturbed in 62% and the galactose index in 80% of the glomerulonephritis cases Bromsulphalein retention was increased in 33% and thymol turbidity was increased in 25% Both the icterus index and Van den Bergh test were normal, while the alkaline-phosphatase figures were in the high normal range

3 *Liver Biopsy*—Examination of many serial sections revealed the presence of foci of disintegrated liver cells, varying in size from

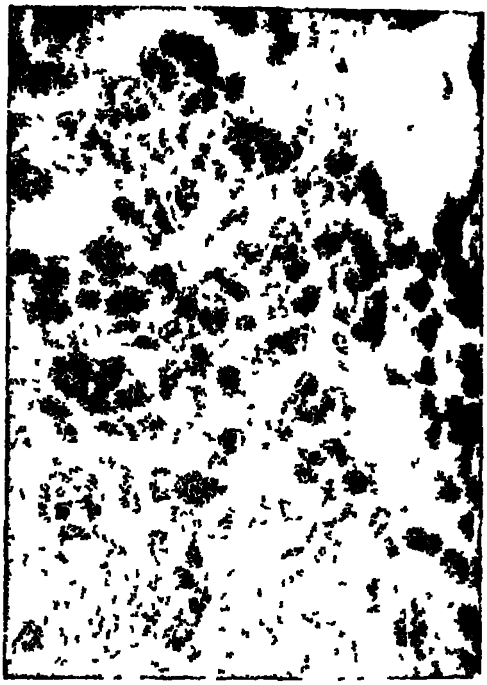

Fig 2—The middle half shows a massive focus, made of several disintegrating liver cells infiltrated by neutrophils and lymphocytes (×450)

small foci (fig 1), made up of one or two liver cells in early cases, to massive necrosis (fig 2) of one or two columns of liver cells in œdema of longer standing These foci were early infiltrated with neutrophils, then lymphocytes, and (in the massive necrosis cases) later fibroblasts and regenerating liver cells around them (fig 3) according to the duration of the œdema, the small foci healed completely The patchy appearance of the liver cells (cuboidal cells alternating with clear globular vaculated cells) denoting possible phases of functional activities, could be confirmed in the specimens studied

The factor responsible for these changes in the liver may be metabolic, the result of disturbed renal function, it may be related to the hypoalbuminæmia or vascular capillaries, or to bacterial emboli not dealt with by the liver because of loss of complement in the urinary protein, or it may be allergic, in view of the response of œdema in some cases to antihistaminic drugs[2] and the fall in the histamine-binding power of the blood in the cases studied

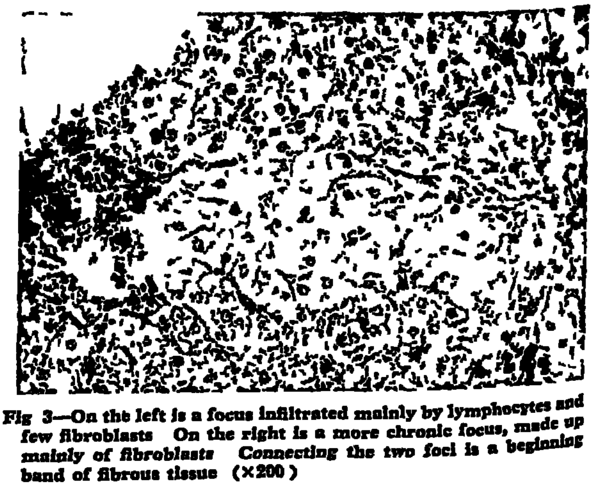

Fig 3—On the left is a focus infiltrated mainly by lymphocytes and few fibroblasts On the right is a more chronic focus, made up mainly of fibroblasts Connecting the two foci is a beginning band of fibrous tissue (×200)

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[1] Boyd, R I *Arch intern Med* 1949, 83, 298

[2] Dorry Loutfy, Kh *J Egypt med Ass* 1951, 34, 755

The possible role of these changes in the production and degree of œdema should be considered

Department of Medicine, KH DORRY LOUTFY

M ESSAM FIKRY

Department of Pathology,
Alexandria University, Egypt M EL-GAZAYERLY

VISITING MENTAL HOSPITALS

SIR,—Mr Woodley's letter in your issue of May 17 highlights the human problem of the long-stay often unvisited patient in our mental hospitals

Fortunately the picture he paints is no longer typical of mental hospitals in England and Wales, where most medical superintendents of mental hospitals welcome and encourage friendly visitors

A summary of replies to a recent questionnaire sent to medical superintendents of mental and mental deficiency hospitals in England and Wales by the National Association of Mental Health shows that visiting of friendless patients by members of voluntary organisations takes place in a majority of hospitals Leagues of Hospital Friends, the W V S, Rotary Clubs, and many women's organisations, such as Women's Institutes and Townswomen's Guilds, do most valuable service in this field

Several medical superintendents have indicated that further help would be welcomed, and this Association would be happy to make available details of any known needs to any responsible inquirers who would like to give help

The National Association
for Mental Health, London, W 1 D MCCLELLAN
Public Information Organiser

SIR,—I felt I must comment on Mr Woodley's letter

At Severalls Hospital we have many such patients whose relatives have ceased to visit for various reasons These patients look forward to visits from members of Women's Institutes, Inner Wheel, &c, who also send letters and gifts to the people they adopt and in suitable cases take them for outings

We are constantly encouraging the lay people to take an interest in our patients, and I am sure other mental hospitals do likewise

Severalls Hospital,
Colchester, Essex R E CLARKE
Matron

AN ALL-IN FAMILY SERVICE

SIR,—In your comments on our new pamphlet, *Families with Problems* (May 17, p 1080), there is an admirable summary of our proposals for a family welfare service You suggest that such a service would not necessarily reduce the number of "callers on the family's doorstep" because the social worker concerned with any family would still be expected to call on specialised help No social worker however can deal with all the medical, psychological, educational, and administrative problems that bedevil some families and he must needs be able to call on, for example, a doctor, a headmaster, a youth employment officer, or the National Assistance Board, for advice and help There is no reason at all why such help should result in more callers

You are evidently concerned lest our proposals would require new legislation You point to the work done by the social workers who have lately been given special responsibility for problem families under certain local authorities The appointment of such workers is a welcome attempt to reduce the duplication and waste of the present multiplicity of social services, but although they do a remarkable job of rehabilitation with many problem families, this is hardly "preventive work" We are naturally pleased at any move which begins to focus attention on "families" rather than on "problems", but we believe that preventive work is only possible when *all* families have access to help with their family problems in their early stages, either by asking for it themselves or by being referred by other agencies who are realising more and more that such matters as overcrowding, truancy from school, cruelty to children, non-payment of rent, and so on contribute to, or are indicative of, family stress Such a service will certainly require new legislation, but social legislation must be expected to keep in step with the awareness of social needs The family is once again being recognised as a most important social unit Legislation for the family must surely not be delayed

SIMON YUDKIN
London, N 3 Secretary, Council for Children's Welfare

PEGGY JAY
London, N W 3 Secretary, Fisher Group

COMPLICATIONS OF RISTOCETIN THERAPY

SIR,—The increasing problem of antibiotic-resistant organisms, discussed in your leading article of March 8, has stimulated the development of a variety of new antimicrobial agents Among the more promising of these has been ristocetin, a lyophilised preparation derived from the fermentation broth of *Nocardia luria*,[1] and marketed under the trade name of 'Spontin' Advantages ascribed to ristocetin have included striking bactericidal activity against gram-positive bacteria and mycobacteria, the lack of development of resistant organisms, and the absence of cross-resistance with other antibiotics[2 3] Reported instances of toxicity have been few, and limited to neutropenia, leucopenia, and local phlebitis at the site of intravenous administration[3 4] Recent experience with ristocetin at Walter Reed Army Hospital has prompted this preliminary report

Results to date have confirmed the potent gram-positive bactericidal properties and the absence of resistant organisms, but they have emphasised the occurrence of toxic reactions especially when the dose of ristocetin was in excess of 50 mg per kg Eight of ten patients in this study developed hæmatological complications, including three cases of acute thrombocytopenia, as well as leucopenia and neutropenia Rash, hyperpyrexia, and local thrombophlebitis were also encountered

While contributing factors may have existed in certain patients, we feel that the complications were attributable to ristocetin Of considerable interest was the profound thrombocytopenia observed in two patients with acute renal insufficiency at a time when urine output was sharply curtailed In one of these the blood level of ristocetin *one week after discontinuing therapy* exceeded by threefold the customary therapeutic level In general, the complications seemed to be due to toxicity rather than individual idiosyncrasy, and they were reversible upon discontinuing therapy or reducing the dosage Subsequently, ristocetin has been used without adverse effects in a dose of 25 mg per kg in two cases

Preliminary experiments with rabbits have provided additional confirmation of the thrombocytopenic effect of ristocetin.[5] In addition, in-vitro studies now in progress have demonstrated a platelet-agglutinating factor,[5] which, together with the finding of a normal bone-marrow in two of the patients with severe thrombocytopenia, suggests a peripheral rather than central toxic action Much more investigation is needed, however, before conclusions can be drawn concerning the mechanism of production of these effects

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[1] Philip, J E, Schenck, J R, Hargie, M F Antibiotics Annual, 1956-57, p 699 New York Medical Encyclopedia New York, 1957

[2] Grundy, W E, Alford, E J Rdzok, E J, Sylvester, J C *ibid* p 693

[3] Romansky, M J, Limson, B M, Hawkins, J E *ibid* p 706

[4] Romansky, M J Personal communication

[5] Gangarosa, E J, Johnson, T R In preparation

Our findings reaffirm the clinical utility of ristocetin, especially in enterococcal and staphylococcal infections, but direct attention to potentially reversible hæmatological complications, including, for the first time, thrombocytopenia In the patients studied, toxicity seemed to be a function of dosage It is suggested that appropriate serial hæmatological studies be performed in all patients receiving this drug, and that extreme caution be observed in those with compromised renal function A more detailed report will follow elsewhere [6]

Walter Reed Army Hospital,
Washington 12, D C

EUGENE J GANGAROSA
Captain, Medical Corps, U S Army

SPONTANEOUS RUPTURE OF THE ŒSOPHAGUS AND BRONCHIAL ASTHMA

SIR,—I was interested to read that Dr Raffle (May 3) had found no previous record of spontaneous rupture of the œsophagus in association with bronchial asthma, for this accident occurred in a patient here last year

An obese male, aged 62, was admitted with an acute exacerbation of his recurrent bronchitis, from which he had suffered for many years He was confused, cyanosed, dyspnœic, and wheezing Improvement followed treatment with antibiotics, intermittent oxygen, and aminophylline, but he remained confused Nineteen days after admission his condition suddenly worsened and he seemed to have had a pulmonary embolus He died within a few hours Postmortem examination revealed right ventricular hypertrophy, a purulent bronchitis, 14 oz of greenish mucoid fluid in the right pleural sac, 4 oz of bloodstained fluid in the left pleural sac There was a rupture of the stomach at the cardiac sphincter

The patient had not vomited before the rupture

I wish to thank Dr E Grahame Jones for permission to report this case

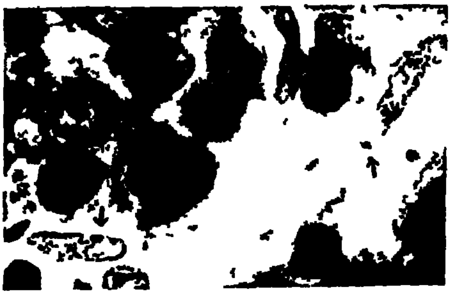
Royal Gwent Hospital,
Newport, Mon

R C R CONNOR

STAINS FOR SEX CHROMATIN

SIR,—According to Lindsay and Barr,[7] "the sex chromatin lacks well-developed argyrophilic properties" and "the accessory body is strongly argyrophilic and refractory to basic dyes, the reverse is true for the sex chromatin"

Forty-six years earlier Ramon y Cajal [8] wrote "Colloidal silver which always resists dyeing of the basophil substances and, strangely, of the nucleinic or chromatic framework of ordinary cells", and "colloidal silver never impregnates any material which is distinctly basophil, much less tissue treated with either neutral or slightly alkaline fixatives (for example, Nissl bodies, the reticulum of nuclein, &c)"



Sex chromatin two fibrocytes in a section of colourless nævus of breast from a woman aged 56 (stained with silver carbonate)

My personal experience is different, and I currently use silver methods in the routine dyeing of sex chromatin in very different kinds of healthy and pathological tissues It is easily done and when the impregnation with silver is good (a result not always obtained) the bright appearance of the cellular picture is entirely satisfactory, especially for photomicrography, because of the excellent contrasts obtained A good example is the accompanying photograph of a malignant tumour

My observations will be published more fully later

Faculty of Medicine,
University of Seville

C BARRIO CUADRILLERO

A STRIPPER ASTRAY

SIR,—An adventure with a vein stripper may be of interest and a warning

In a very obese woman, a high resection and "flush tie" of the long saphenous vein at the saphenous opening was performed A *Myers*-type stripper was introduced in the long saphenous vein in front of the medial malleolus with the object of stripping out the vein It passed up very easily except for a slight check in the mid-calf A moment too late it was realised that the tip of the stripper had not appeared in the saphenous vein at the upper incision The stripper could be palpated in the femoral vein at the saphenous opening, the tip being higher up Gentle pulling failed to extract the stripper, the tip of which seemed to be caught or jammed above the inguinal ligament Pulling was tried with the leg in all possible positions, and the patient was tilted feet down to distend the veins, but still the stripper would not come

It seemed almost certain that the external iliac vein would be torn if the stripper was forcibly pulled Therefore an extraperitoneal exposure was made above the inguinal ligament The stripper was immediately found impacted in a small vein in the extraperitoneal fat $1^1/_4$ in above the inguinal ligament This vein appeared to be a small tributary of the external iliac vein The little vein was divided, and the tip of the stripper pushed through and cut off with wire cutters The stripper was then easily withdrawn and the ends of the vein tied The operation was completed by closing the incisions and the short saphenous vein was ligated behind the knee The patient recovered uneventfully, and there was no evidence of postoperative deep-vein thrombosis

The lesson to be learnt from this case is that the operator should always know exactly how far up the leg the tip of the stripper has travelled It is known that a stripper can enter the deep veins through one of the communicating veins, but I have never heard of any difficulty in pulling the stripper back again It must be very rare indeed for a stripper to enter the deep veins and then escape through a tributary, though the angle of junction just above the inguinal ligament might favour this Usually the stripper can be felt in its passage all the way up the long saphenous vein, and often, in thin people, it can be seen through the skin as well In obese people it can be very difficult to follow the course of the stripper, which could enter the deep veins without the operator's knowledge Perhaps the easiest way to be certain how far the stripper has travelled is to have another stripper of exactly the same length at hand so that the distance can be measured

The predicament described here occurred very easily and simply The consequences could have been serious if the stripper had been pulled too forcibly The importance of knowing the exact position of the tip of the stripper cannot be too strongly emphasised

Tottenham Hospital Group,
London, N 15

E E O'MALLEY

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[6] Gangarosa, E J , Landerman, N S , Rosch, P J , Herndon, E G In preparation

[7] Lindsay, H A , Barr, M L *J Anat , Lond* 1955, 89, 48

[8] Ramón y Cajal, S *Trab Lab Invest Biol Univ Madr* 1910, 8, 27

RESIDENTIAL CHARGES ALLOWABLE AS INCOME-TAX EXPENSES

SIR,—I have recently been successful in a claim, to H.M. Inspector of Taxes, for residential charges to be allowed as expenses, and since I am sure this will apply to many others I feel it should be made known generally.

Where a married house-officer, senior house-officer, or registrar maintains accommodation for his wife, and holds a post which necessitates his being resident, a deduction, under paragraph 7, ninth schedule, Income Tax Act, 1952, will be allowed of the total additional expense for board and lodging which is incurred by him in the performance of his duties.

I hope others affected by this will find it helpful news.

Kent and Canterbury Hospital,
Canterbury.

E. A. HARVEY-SMITH.

A SAFER WEEDKILLER

SIR,—Your columns have often carried justifiable warnings of the potential risks run by farmworkers and spraying operators in the use of the toxic herbicides dinitro-o-cresol (D.N.C.) and dinitro-butylphenol (dinoseb). D.N.C. has caused 8 of the 11 fatal cases of pesticide poisoning in Britain since 1946. Unfortunately, farmers cannot control all weeds in their cereal crops by using the non-hazardous "hormone" weedkillers such as 2,4-D and M.C.P.A. After a few seasons, "hormone-resistant" weeds accumulate, and a stronger weedkiller is needed. Although D.N.C. has been safely used to control hormone-resistant weeds for the past six years, neither this chemical nor farmworkers have changed their characteristics, and the potential risks remain. The pesticide industry has therefore continued to seek safer herbicides with broader spectra of use against weeds in corn, and several material improvements on 2,4-D and M.C.P.A. have become available in recent years.

The most recent development is trichlorobenzoic acid (T.B.A.), which, when added in quite small amounts to existing M.C.P.A. weedkillers, will kill or effectively control five increasingly common hormone-resistant weeds in corn—i.e., heriff (cleavers), mayweed, redshank, chickweed, and knotgrass. Hitherto many thousands of acres of corn have been treated with D.N.C. simply because these weeds were present and predominant.

The toxicity of T.B.A. has naturally been studied with much interest. It can exist in several isomeric forms of varying herbicidal activity. Their acute oral toxicity in laboratory animal species is low, LD_{50} values ranging from 300–1500 mg. per kg. depending on species, compared with 25–80 mg. per kg. for D.N.C. The most herbicidal isomers are among the least toxic to mammals. The oral LD_{50} of T.B.A. in the pheasant is about 1 g. per kg., and in the hen over 1.5 g. per kg. Percutaneous toxicity in the rat is extremely low, 1000 mg. per kg., applied for twenty hours under an impermeable covering, caused no toxic effects.

The cumulative toxicity of T.B.A. was tested by dietary feeding trials with rats lasting two months. Even 10 000 parts per million in the entire diet caused no mortality or obvious toxic effects, although there was histological evidence of cellular injury in liver and kidney. These effects were also present to some extent at 1000 p.p.m., but negligible at 100 p.p.m.

In all, fourteen isomers of di-, tri-, and tetra-chlorobenzoic acids have been examined, and all had low toxicity in mammals. Their presence as manufacturing impurities would therefore not decrease the safety of T.B.A. in agricultural use.

These isomers differ not only in their mammalian toxicity but also in their apparent mode of toxic action. Some of them caused an unusual "myotonic" effect even at non-lethal doses, the animals showing transient but severe muscular rigidity on handling. Other isomers failed to produce such myotonic effects, even at lethal doses. This type of myotonic response has already been described as one of the toxic effects of 2,4-D,[1] and is similar to that producible by veratrine alkaloids, 9-phenanthoate, and dihydronaphthacridine.[2] Details of the toxicological studies carried out on T.B.A. and its analogues will be published elsewhere.

Laboratory investigations are not always a reliable indication of risks in the field. Observations made during experimental trials in 1956–57, in which over 4000 acres were treated with various T.B.A. mixtures by farmers, spraying operators, and research-workers do, however, support the implication that T.B.A. is virtually non-hazardous in use. No reports were received or evidence brought forward of adverse effects among users, farmstock, bees, wildlife, game, or fish.

The problem of selective weedkilling in farm crops is still far from solved, despite the advances which are occurring. It will still be necessary to use the toxic dinitro-herbicides for weed control in some pea crops, or where cereals are undersown with clover. Nevertheless, it is just as pleasing to the pesticide industry as to the pharmaceutical industry when a new development, such as T.B.A., combines the virtues of effectiveness and every promise of safety in use.

Chesterford Park Research Station,
near Saffron Walden, Essex.

E. F. EDSON.

DISPLAYING AXILLARY LYMPHATICS IN MASTECTOMY

SIR,—Many cases of lymphœdema of the arm following radical mastectomy and X-ray therapy are referred to me. I find these patients difficult to help and the operation I do gives only limited relief.

One feels that damage to the arm lymphatics during operation is the primary cause. Lymphœdema occurs more commonly in fat women than in thin, so greater care should be taken in the fat than in the thin in the extent of the axillary dissection. I will not go into the relative merits of radical mastectomy as opposed to local mastectomy in the cure of breast carcinoma, but to me the development of lymphœdema is a contra-indication to the bigger operation.

Obviously to avoid damage to arm lymphatics and at the same time to remove the breast lymphatics from the axilla, a method of showing these different lymphatics in the axilla is of great value, and this can easily be done by injecting 2.5 ml. of 11% patent blue into the subcutaneous tissue of the arm. Alternatively, a similar injection into the breast by the nipples will show the breast lymphatics. These injections give a most dramatic visualisation of lymphatics, and I would urge any surgeon who is doing a mastectomy to inject 2.5 ml. of patent blue into varied sites, some ten minutes before operating, injecting, in successive patients, into the subcutaneous tissue of the arm, intramuscularly into the arm, subcutaneously over the breast, intramammarily by the nipple, and between the growth and the axilla. Of these, the interesting one is the intramuscular injection of the arm which often shows no drainage via axillary lymphatics! I am in process of collecting data with a view to publication, unless I find that somebody has already done so. However, I would urge any practising surgeon to visualise for himself the lymphatics in the axilla, and he will note at once how many important arm lymphatics pass through the apparently useless axillary fat that lies above the vein. One warning—he should inform his anæsthetist because the patient goes a ghastly blue for several hours.

London, E.1.

CHARLES HEANLEY.

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1. Bucher, N. L. R. *Proc. Soc. exp. Biol., N.Y.* 1946, 63, 204.
2. Krayer, O., Acheson, G. H. *Physiol. Rev.* 1946, 26, 432.

Parliament

Pollution of Rivers

The 1951 Act entrusts the defence of our rivers against pollution to the river boards, but it includes a proviso that for seven years the boards can only bring proceedings in respect to the discharge of trade effluents or of effluents from local authority's sewage works with the approval of the Minister of Housing and Local Government. The Act also makes provision for the extension of this period by Order in Council, and on May 17 Mr J. R. Bevins, parliamentary secretary to the Ministry, asked for its extension for another three years. The temporary restriction of the boards' powers had been imposed, he reminded the House, because it was feared that without some control over prosecutions, we might have been forced into capital expenditure which the country could ill afford. In the event, however, the river boards had been confronted with technical obstacles which so far had prevented them from devising byelaws laying down permissible quantity and quality standards for effluents. Against this background the Minister had asked the Central Advisory Water Committee whether the seven-year period should be extended and they had recommended that it should be extended by a further three years.

Since the 1951 Act became law, Mr Bevins recalled, there had been 25 applications for the Minister's consent to prosecute. Consent had been given in 7 cases and fines had been imposed by the courts. In the remaining 18 cases, the applications for consent to prosecute were withdrawn while remedial measures were being taken, and 5 of those were still under consideration. In only 1 case was consent to prosecute refused by the Minister. If the seven-year period was allowed to expire it would then be open to anyone alleged by a river board to be causing pollution to plead in defence that it was not reasonably practicable to dispose of the effluent other than by discharging it into the stream, and secondly, that all reasonable and practical steps had been taken to make the effluent not poisonous or noxious. If the court accepted that plea, then the person alleged to be responsible would not be liable to any penalty. This broad provision in the 1951 Act has been in suspense during the last seven years and would remain in suspense if the period of control was prolonged. Thus though the termination of the period might make it easier for the river boards to put pressure on alleged offenders, they would find it more difficult in cases of prosecution to sustain their argument before the court. But Mr Bevins added that he would not disguise for a moment that the fundamental difficulty was money. So long as we had restrictions on capital expenditure which might prevent the extension of sewage treatment works we could not ignore the fears of those in industry lest they should be caught between the difficulties of capital restriction on the one hand and prosecution on the other. The Minister was not in any way complacent about this problem: where he could he was authorising capital expenditure for sewage treatment works and sewage disposal. Since the war, schemes costing more than £200 millions had been sanctioned and there had been a steady increase in the last few years.

Members were less happy than Mr Bevins about the proposed extension. Mr Anthony Greenwood, as a representative of one of the dirtiest rivers in the country, viewed it with a good deal of dismay and suspicion. He suggested that it would in fact defer for another three years the granting of adequate powers to the boards. Though so much money had been spent on sewage schemes, improvement had not been rapid because towns were taking more and more water out of rivers above the town and putting back water into the river in the form of inadequately treated sewage below the town. The flow of many of our rivers had been seriously reduced. Until we had a national water plan this situation would continue. The Ministry which was responsible for curbing development of sewerage schemes was at the same time allowing water authorities to deplete our streams. During the three extra years now asked for our streams would continue to be polluted and there could be serious possibility of a grave epidemic. He reluctantly assented to the proposal, but thought that there should be no further extension and that the Ministry should really get down to the job of seeing that the river boards could discharge the task which had been entrusted to them.

Mr Edward Short said that the River Tyne had been described as an open sewer. Surely it could not be healthy to have this great sewer running through the middle of a densely populated industrial area. As he understood it, the local authorities were under no obligation, so long as the immunity existed, to find alternative methods of disposal, and they were under no obligation to render the effluent innocuous. Yet no part of the country was far from the sea. It was simply a question of money to take the industrial waste or sewage to the sea. Every year great new housing estates arose, and every year new industries developed with new and more deadly kinds of waste. In the future we might have nuclear waste discharged into our rivers.

Mr Bevins agreed that in certain areas there had been some deterioration in the state of our rivers. But the question was whether the removal of Ministerial consent would help to lessen pollution, and whether this would be the right time to remove that consent. He submitted that it would be unreasonable, at this stage, to expose people to the risk of prosecution when control over capital investment might be holding back the construction of modern sewage works through which most industrial effluents should pass. The figures for capital investment in sewerage works since the war did not support the view that the Government had been neglecting their duty. There was no evidence of a single scheme put up by a local authority which had been turned down, if it was essential in the interests of health.

The House agreed to ask for an extension.

QUESTION TIME

Suicide and the Law

Mr Kenneth Robinson asked the Home Secretary what further consideration he had given to the legal aspect of suicide and attempted suicide, and if he was aware that the law of England and Wales stands almost alone in regarding such acts as criminal.—Mr R. A. Butler replied: I am pursuing my study of this problem, which has practical aspects of no less importance than its legal aspects. I am not yet ready to reach a conclusion upon it. Mr Robinson: Is the Minister aware that a joint committee, set up by the *British Medical Association* and the Magistrates' Association, has reported in favour of a change in the law? In view of this weighty opinion, will not the Home Secretary make an early decision in this matter?—Mr Butler: I am aware of the report. I am also aware of various other considerations. I think this is a very difficult subject, but I will undertake to consider what the hon. gentleman has said.

Mr Gordon Walker: Would not the Minister agree that this is a matter which needs as early consideration and decision as possible? Would not he also agree that there are no real religious grounds for our law as to attempted suicide, and that this was due to a judicial decision about a hundred years ago? Is there not a great deal to be said for bringing our law into line with that of other countries?—Mr Butler: I have carefully studied the position in other countries and also the statistics of the convictions. For example, in 1956, proceedings were brought in 613 cases out of 5000 or more, and over 90% of these charges resulted in probation for the person concerned, and very few in sentences of imprisonment. I have also considered that in a minority of cases, without the power we have now, we might not be able to achieve the desired results, so that, on the facts, it is a very difficult question to decide.

Mr Robinson: Does not the Minister agree that other provisions of the law in regard to breach of the peace and mental health are quite sufficient to deal with the cases he has in mind?—Mr Butler: The Government's approach to mental health is at present actual, and does bring all this subject to the fore. It is against that background that I am examining it.

Wolfenden Report

Mr D L **Donnelly** asked the Home Secretary whether he was yet in a position to make a further statement regarding the Government's policy towards the Wolfenden report on homosexuality and prostitution —Mr **Butler** replied Many representations have been made since the report was published Some of them are in support of the committee's recommendations, but others are strongly critical This applies both to the main recommendations on homosexual offences and to those on prostitution It is clear that the committee's recommendations have stirred public opinion widely and deeply, and I would not propose to decide on a future course of action until that opinion has had the fullest opportunity of expressing itself

Composition of Milk Committee

The Minister of Agriculture, Fisheries, and Food has set up a committee

> To consider the composition of milk sold off farms in the United Kingdom from the standpoint both of human nutrition and of animal husbandry and to recommend any legislative or other changes that may be desirable

The chairman will be Dr J W Cook, vice-chancellor of Exeter University, and the 14 other members include Dr D P Cuthbertson, Dr Philip Evans, Dr H E Magee, and Prof B S Platt

Scientific Research

The Lord President of the Council has set up a committee, under the chairmanship of Sir Claude Gibb, with the following terms of reference

> "To inquire into the techniques employed by Government Departments, and other bodies wholly financed by the Exchequer, for the management and control of research and development carried out by them or on their behalf and to make recommendations "

The five other members include Sir Solly Zuckerman, professor of anatomy in the University of Birmingham

Obituary

Prof GEOFFREY RAKE

S C L writes

Surely a measure of the impact of a personality is the vividness of a memory recalled from afar I was a "clinical" with Geoffrey Rake in our first post-qualification appointment, and although I did not know him well then or at any time, he still looms out in strong silhouette against the misty background of his colleagues—and, for that matter, of most of his mentors

It was as a student that he did his meticulous work on achalasia of the cardia—a fragment of research that would have done credit to an experienced postgraduate He was serious, shy, meticulous, and obsessional, with bursts of gaiety I remember him best for one incident. After a bedside dissertation by a senior physician on the colour of the conjunctivum as an assessment of the hæmoglobin value, we were all made to examine a patient, and we guessed wildly in turn But Geoffrey Rake peered down for what seemed an interminable time into the eye of the patient, stood up, said "Eighty-five per cent," then reflected and said, "No, eighty-three per cent" Much as I would like to report that his considered opinion was correct, I cannot, for there my memory returns to the mists

Births, Marriages, and Deaths

DEATHS

Coates—On May 24 at Bridgwater Hospital, Somerset. John Francis Coates, M D M R.C.P, aged 50, husband of Eve, only son of Dr Richard Coates of Burnham, Somerset.

Notes and News

EDUCATION IN HEALTH AND NUTRITION

In many underdeveloped countries much of the new medical science cannot benefit the people until they have learnt something of the general principles that cause diseases to spread How such knowledge is best given was discussed at a seminar[1] in Baguio, in the Philippines, organised by the Food and Agriculture Organisation and the World Health Organisation, in October, 1955 It was attended by over 70 people, doctors, educationists, home economists, social workers, and others from many countries in Asia and it was directed by an international staff

The report is written by one of the delegates A single authorship allows a more lively style and outspokenness than is possible when, as in so many international reports, many authors are jointly responsible There is, for instance, a detailed criticism of the organisation and planning of the seminar This is useful, for the seminar itself was a major new venture in education, and future international seminars can profit from the experience gained Although, with a large subject, the discussions were necessarily diffuse, a few general principles emerged

1 No educational programme can be effective unless it is based on a knowledge of the way of life of the people and their own desires and ambitions Their beliefs, behaviour, attitudes towards health and disease and towards food must first be studied This can only be done by living amongst the people in their village

2 Education must have well-defined goals and objectives These must be expressed specifically for the areas in which it is hoped to bring about a change and must be stated in terms suitable for operations in small villages Full consideration must be given to the wishes of the community and the programme must be designed to fulfil needs felt by the people themselves In drawing up plans it is necessary to consult doctors and other health workers, educationists, economists, and agriculturists and, most important of all, local community leaders The recognition of such leaders and the enlistment of their cooperation is an essential preliminary

3 The techniques of education applicable for children in schools may be useless for adults In particular didactic teaching is of limited value Demonstrations are to be preferred and every effort made to involve as many members of the village as possible in the demonstrations Adult teaching is best based on groups with a common interest, which already exists in a community

Much health education in the past has been unprofitable owing to the use of techniques unsuited to the local community If waste of effort and money is to be avoided, a careful attempt at evaluation of the results of an educational programme must be made Such evaluation should not be left till the end, but should be made periodically to find out whether the programme is developing as planned

There is much valuable detail in this report, and all concerned with promoting the health and welfare of village life in the tropics will be able to learn something of value from it

INITIAL SALARIES OF CONSULTANTS AND S H M.O s

The Minister of Health (H M [58] 38) has asked hospital boards to take account of a submission by Committee B of the Medical Whitley Council The committee points out that, under the Terms and Conditions of Service of Hospital Medical Staff, consultants and senior hospital medical officers appointed at age 32 or over are to be paid under incremental scales, subject to the discretion given to boards to fix the starting salary up to four incremental points above the minimum (1) by reason of age, special experience, and qualifications, or (2) by reason of age alone, where seniority has been lost because of service with the Forces Committee B reports that a higher proportion than might have been expected have on appointment been placed at the minimum point on the scale The committee says that boards should consider exercising their discretion in each case on merit, and it suggests that boards might look for advice to the Advisory Appointments Committee

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[1] Report on an International Seminar on Education in Health and Nutrition By F W Clements (1956) F A O Nutrition Meetings Report Series no 13 Obtainable from H M Stationery Office Pp 91 5s

University of London

On Nov 21 the honorary degree of LL D will be conferred on Sir Archibald Gray

University of Leeds

Dr M D Sumerling has been appointed a research fellow in radiodiagnosis

University of Edinburgh

The following appointments have been made Dr Lowell Lamont, Dr Samuel Lipetz, and Dr J E Margaret Munro, part-time lecturers in the general practice teaching unit, Dr Donald Michie senior lecturer, and Dr J G Howard lecturer, in surgical science

Mrs Amy McGhie of Keswick has bequeathed half of the residue of her estate (estimated at over £13,000) to the university to set up a fund for research into mental and nervous disorders

Royal College of Physicians of London

On Tuesday, June 10, at 5 P M, at the college, Pall Mall East, S W 1, Dr J N Morris will give the Ernestine Henry lecture, on coronary heart-disease and occupation

Royal Society of Health

Lord Cohen of Birkenhead has been elected president of the society

Cleaner Rivers

Addressing the River Boards' Association on May 16, Mr Henry Brooke, Minister of Housing and Local Government, said that " within the not too distant future we are going to see a quite outstanding improvement in our rivers, and my aim is to make their amenity value and their recreation value match their utility value" Though the River Boards Act of 1948 and the Rivers (Prevention and Pollution) Act, 1951, give effective powers for dealing with river pollution, it had not yet been possible to find more than a part of the huge amount of money needed to overcome the neglect of over a century Nevertheless, since the war, local authorities had spent more than £205 million on sewerage and sewage disposal, the greater part on disposal works bound to benefit the rivers into which effluents were being put In 1957—a difficult year—£28 million of works had been authorised by the Ministry, against £15 million in the preceding year and a pre-war average of £$5^1/_4$ million On top of this were the very large sums spent by industry on pre-treatment of trade effluents " Improvement and restoration must be a gradual process The task we have to tackle jointly is to determine, from time to time and from place to place, what limits of pollution are to be tolerated, and then to endeavour over the years to reduce those limits " Members of the Government had to find a balance between the many demands on the country's capital resources, and a balance too between the interests of urban and industrial development (which necessitated effluent disposal and sometimes water abstraction) and of those who enjoy the countryside and the fishing, who rightly and forcefully criticised and opposed them

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The Central Middlesex research prize for 1958 has been awarded to Dr David Phear

Mr A R Horsham has been appointed secretary of the Royal Institute of Public Health and Hygiene

Sir Kenneth Cowan is to lead the United Kingdom delegation to the eleventh World Health Assembly, which is being held at Minneapolis from May 25 to June 14

At the inauguration of the new buildings of the Medical Society of the University of Aix-Marseilles, the honorary degree of M D was accorded to Dr Macdonald Critchley

Prof E G L Bywaters leaves on June 3 for Yugoslavia where he is to lecture on the prevention of rheumatism His lecture tour, which is sponsored by the British Council, is being made at the invitation of the Yugoslav Union of Medical Societies through the National Commission to UNESCO

The Leeds Medical Exhibition will be opened at the Town Hall, Leeds, at 2 45 P M on Monday, June 2, by Prof S J Hartfall It will remain open till June 6

Diary of the Week

JUNE 1 TO 7

Sunday, 1st

UNIVERSITY COLLEGE HOSPITAL, Gower Street, W C 1
10 15 A M Dr W R Trotter Thyroid Diseases (Lecture demonstration for general practitioners)

Monday, 2nd

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY, Chelsea Hospital for Women, S W 3
4 30 P M Mr Frank Denny Postoperative Complications in Gynæcological Practice

Tuesday, 3rd

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W 12
4 P M Dr Howard Burchell (Rochester, Minnesota) Uncommon Heart Diseases

INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Dr R H Meara Bullous Eruptions

Wednesday, 4th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
5 15 P M *History of Medicine* Mr Adrian Hill The Patient with the Paint Brush

POSTGRADUATE MEDICAL SCHOOL
2 P M Prof C P Beattie Toxoplasmosis

INSTITUTE OF DERMATOLOGY
5 30 P M Dr Henry Haber Histopathology of Vesicular and Bullous Eruptions

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P M Dr P J Lawther Air Pollution and Disease

INSTITUTE OF CARDIOLOGY
5 P M (1, Wimpole Street, W 1) Dr Howard Burchell Pulmonary Hypertension in Congenital Heart Disease. (St Cyres lecture)

MEDICO-CHIRURGICAL SOCIETY OF EDINBURGH
8 30 P M (18, Nicolson Street, Edinburgh) Mr G A Pollock The Spastic Child

Thursday, 5th

ROYAL SOCIETY OF MEDICINE
5 P M *United Services* Surgeon Commander Stanley Miles, Surgeon Lieut -Commander J S P Rawlins, Surgeon Lieutenant R J W Lambert Underwater Emergencies

POSTGRADUATE MEDICAL SCHOOL
4 P M Dr R Bodley Scott Treatment of Leukæmia

NUFFIELD ORTHOPÆDIC CENTRE, Wingfield-Morris Orthopædic Hospital Oxford
8 30 P M Dr A M Cooke A Physician looks at Fractures

HONYMAN GILLESPIE LECTURE
5 P M (University New Buildings, Teviot Place, Edinburgh) Dr Thomas Anderson Respiratory Infections in Early Childhood

Friday, 6th

POSTGRADUATE MEDICAL SCHOOL
10 A M Mr I W MacPhee Observations on the Genesis of Traumatic Shock
2 P M Sir James Learmonth Biological Reserves in Man

ST MARY S HOSPITAL MEDICAL SCHOOL, Paddington, W 2
5 P M Mr Philip Rhodes Prolapse of the Cord

Saturday, 7th

ROYAL SOCIETY OF MEDICINE
10 A M *Dermatology* (General Infirmary, Leeds) Prof W T Astbur Advance of Molecular Biology
2 P M Prof Gustav Riehl (Vienna) Tuberculosis of the Skin Social Aspects

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
10 A M (Hammersmith Hospital, Ducane Road, W 12) Prof Ian Donald Neonatal Respiratory Problems

Appointments

BOREHAM, P F, M CHIR Cantab, F R C S consultant surgeon, North Gloucestershire clinical area

FLOOD, C M, M D Lond, M R C O G honorary assistant obstetrician and gynæcologist, Hospital of St John and St Elizabeth, London

KEITH, MARJORY A, M D Edin, F R C P E part time consultant physician, Bruntsfield and Elsie Inglis Hospitals, Edinburgh

ROBERTSON, R F, M D Edin, F R C P E consultant physician, Longmore and Deaconess Hospitals, Edinburgh

ROBINSON, J O, M CHIR Cantab, F R C S part-time consultant in general surgery, St Bartholomew s Hospital, London

TODD, I P, M S Toronto F R C S part-time consultant in general surgery, St Bartholomew s Hospital, London

The Hospital for Sick Children, Great Ormond Street, London

EASTWOOD, ROSALIE E B, M B Glasg resident officer, departments of neurology and neurosurgery

NEWMAN, C G H, M B Lond, M R C P, D C H house physician

WHITE, R H R, M B Cantab, M R C P, D C H medical registrar and pathologist

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CORRIGENDUM *Pre-eclamptic Toxæmia* —In the letter by Professor Gray and Dr Rinsler (April 12, p 794) reference 4 was incorrect It should have read Migeon, C J, Bertrand, J, Wall, P E *J clin Invest* 1957, 36, 1350

The Lancet · Saturday 7 June 1958

THE PLACE OF HUMAN BIOLOGY IN MEDICAL EDUCATION

SUGGESTIONS FOR A REVISED PRECLINICAL COURSE IN THE LIGHT OF THE GENERAL MEDICAL COUNCIL 1957 RECOMMENDATIONS *

J M Tanner
M B, Ph D, D Sc Lond, M D Pa, D P M
SENIOR LECTURER IN GROWTH AND DEVELOPMENT, INSTITUTE OF CHILD HEALTH, UNIVERSITY OF LONDON †

How one trains medical students depends on what view one takes of medical practice Furthermore, as every teacher of the so-called basic medical sciences experienced in spreading pearls before the jaundiced eyes of students hell-bent on doctoring will agree, how the medical student trains himself depends on what view *he* takes of medical practice

If teacher and student think of practice primarily as the mending of broken bones, then they will think of training primarily as anatomy plus surgical technique, with a little pathological physiology and a little bacteriology thrown in If they think of practice primarily as treating patients with heart-disease, they will think of training as physiology plus pharmacology, one hopes with a little patience thrown in If they think of practice as condemning slums, purifying water, and destroying mosquitoes, they will think of training as bacteriology and parasitology with a little engineering thrown in

But if they think of medical practice as an endeavour to understand individual people in relation to their hereditary endowment, their upbringing, their family, their social position, and their whole culture, and as an endeavour to guide them, so far as may be, from childhood to old age through the squalls and doldrums so that they slip as seldom as possible over that invisible equator which divides health and disease, whether of mind or body, if they think of medicine as such an attempt, such an activity, how *then* do they think of training? Certainly *not* as a series of scarcely connected courses in physics, chemistry, anatomy, and physiology culminating in instruction by a multitude of specialists each on how to be an elementary specialist in his own particular field—though this, with little amelioration, is our almost universally practised system Fundamentally, of course, their thinking depends on what view teacher and student take of the nature of man, and of man's place in Nature I need scarcely remind you—but I am certain we must continually remind many others—that this year is the Darwin centenary

It is my thesis here that the practice of medicine as it is developing in European and American cultures, and perhaps throughout most of the world, is most usefully thought of as *applied human biology* Taking a strictly naturalistic and post-Darwinian view of man, doctors should be thought of as applied human biologists, and this in exactly the same sense in which we currently use the words "applied biologist" when discussing the role in society of the pest-control officer By this I do not wish to imply a one-sided belief in negative eugenics coupled with a despairing cynicism for our species! Nor do I mean in any way to overlook or displace from priority the duty of the doctor to cure, when sick, the individual patient I mean quite simply that the applied biologist, from pest-control officer to game-warden, is a recognised figure who helps us understand and control the numbers, ecology, behaviour, disease, and individual welfare of various species from bedroom pests to big game

That the applied human biologist should do likewise is, I am aware, a great claim It is not quite so great a claim as may appear at first sight, the *policy* of the applied biologist—whether we want more or less big game and so forth—is determined, at least in theory, by Governments and not by the biologist His role is that of adviser and implementer Similarly with the doctor as I see him, only here the superior authority is the culture itself, or its arbiters—Government, the Law, religion, and the organs of public opinion I am thus not claiming for him the role of ruler (though Heaven knows we might do worse than stake such a claim in our present confusion), but I am claiming a very wide field of operation as adviser and implementer

To tell the truth the doctor is already in one guise or another occupying most of the field The general physician is taking over increasingly the advisory (as distinct from absolutional) role of the priest, the psychiatrist is continually battering at the ramparts of the Law Abnormal behaviour is now as much their province as abnormal physiology Thus there is nothing in the slightest revolutionary or even new in what I am saying I only wish to make the point that we have not yet fully recognised the situation, or at any rate have not recognised it sufficiently to reflect it in our medical curriculum

If doctors are applied human biologists, then their basic training, before the clinical application, should be in human biology The orientation of their course should be analogous to the orientation developed for the animal biologist by J Z Young in his magnificent new textbooks *Life of Vertebrates* and *Life of Mammals* What we need is a *Life of Man*

The Place of Studies of Growth and Constitution in the Curriculum

It is against this background that I see the place in the curriculum of the studies of human growth and human constitutional variation Both are basic ingredients of a curriculum on the lines I envisage, and both should be taught early and to all medical students, and not late and to a few specialists, as is almost universally the case now The biological facts of human growth (and, of course, decay) provide the best possible background for the study of the family, the social group, and the variety of subcultures which the student should certainly engage in The life-cycle orientation, the study of growth and senescence, would also, I believe, be the answer to all modern educators' prayers—how to fuse the separate disciplines of anatomy, physiology, pathology, &c, without introducing a philosophical artificiality which carries the elements of its own disruption It is perfectly clear to everybody, though intensely disliked by all (except students) that the details of all our present subjects must be omitted at the undergraduate non-specialist stage, I am *not* suggesting that they be replaced by the details of the growth process I am suggesting that the passage of time, the biological principle itself, be used as the binder of diverse approaches, techniques, and disciplines

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* An address written for the Ciba Symposium on The Scope of Physical Anthropology and Human Population Biology and their place in Academic Studies (November, 1957) on the requested theme The Place of Studies of Human Growth and Constitution in Medical Education

† Working at the Child Study Centre of the Institutes of Education and Child Health

As for human constitution, I envisage it as the basic common building material out of which are fashioned the different cultures and subcultures erected by men in various times and places If we are to understand the variety of these cultures and subcultures, and if we are to envisage accurately the possibilities of cultures struggling for birth, then we must know, and must teach, all we can about the nature and variety of our basic material

Giacinto Viola, professor of medicine at Bologna, and perhaps the greatest constitutionalist of this century, defined his subject as " the science of individual variations and nothing else ", and constitution as " the total of all the morphological and functional characters by virtue of which an individual differs from other individuals " If we compare this statement with J B S Haldane's definition of genetics as " the branch of biology which is concerned with innate differences between similar organisms " we see that the only difference between the two statements lies in the word " innate " The majority of constitutionalists do not wish to be restricted absolutely to the study of innate differences, but this is very largely because in the human the contributions of heredity and environment are so difficult to disentangle

I need hardly remind you of the wide disparity between this view of the place of growth and constitution in the curriculum and its actual position, which is practically non-existent At present very few departments of anatomy teach anything worth while, or indeed anything at all, about human growth A small fraction of the life cycle may be touched upon in the embryology course, it is true, but if life begins at 40, or even at 40 weeks, then most anatomical departments still slumber secure in the womb of tradition

There are signs that quickening has occurred, however It is significant that in the newest British textbook of anatomy a chapter on growth appears for the first time Certainly it is by far the shortest and least detailed section of the book, and it is illogically placed at the back end, thus giving something of the impression of a movie run backwards to any occasional student who manages to get that far after his studies of adult detail, nevertheless, it is there

The teachers of undergraduate pædiatrics, with one or two significant exceptions, do little to amplify the student's basic knowledge of growth They serve a small and relatively newly arrived specialty and they have little teaching time even for their strictly medical problems Usually they content themselves with a lecture or two on behavioural development during the first few years of life At least two American textbooks of pædiatrics, however, have quite long and excellent chapters on growth and development, it is to these I have to refer my post-gradute students, who arrive for their specialist pædiatric training at the Institute of Child Health for the most part, knowing, I am sorry to say, virtually nothing at all about how children grow

The teaching of human constitutional variation—morphological, physiological, and behavioural—is equally, but more understandably, neglected Studies of constitution at the undergraduate level must naturally be bound up with human genetics, and this is a subject that has made as yet little headway in most medical schools Though a considerable number of anatomists have genetical leanings, the great majority of professional physiologists are quite uninterested in and uninformed about the subject, perhaps the physiological aspects of constitutional differences have more hope of entering the curriculum through the agency of the chemical pathologist As it is, only when they reach their course in psychiatry do students meet constitutional conceptions, the tradition of Kretschmer, and the relative clarity of the relations between physique and mental disorder in a field where objective relations are so few, still sees to that

A New Preclinical Curriculum

With some temerity but very sincerely, I suggest that the preclinical medical course ought to be remodelled and unified into a course on the *Life of Man* Coming down to brass tacks, just *how* could the early part of the curriculum be remodelled ? Just how could the idea of the maturing process, the passage of time and the acquisition of experience in the life of the organism, be used to cement together our presently scattered bricks ?

The First Part

The first part of the course may be called *Cellular Biology* It would last certainly three whole terms, possibly four or even five We assume a universal background of elementary (i e , General Certificate of Education) English, mathematics, physics, chemistry, and biology We assume also for some students advanced G C E level in three subjects, which personally I believe should be English and mathematics compulsorily, together with one other, preferably chemistry, physics, or biology But most students would enter medical school at 17, not 18, since the entire course to qualification occupies six years

The lines of the cellular biology course are fairly obvious, bearing in mind that structure and function are to be strictly integrated (which is as easy at the cellular level as it is sometimes difficult at later stages in the course), and that biochemistry, genetics, and evolution are to be made similarly inseparable in the student's mind Pathology—i e , cellular pathology—is introduced right from the start every function can go wrong, and when we know the result of any particular going wrong in terms of cellular or medical disease, we describe it It is a very short step from the genetical biochemistry of *Neurospora* to the fundamental lesions of sickle-cell anæmia, alkaptonuria, and beriberi Behaviour also is introduced from the start, ethology will be our constant companion throughout the course until it leads without any break into human behaviour as developmental human psychology, sociology, and anthropology

Thus, for example, we begin by describing the appearance and histochemistry of relatively unspecialised mammalian cells, together with the biochemical energetics by which they maintain their structural integrity, and fulfil their particular function Alteration in function conditioned by genetic changes leads to a study of chromosomes, the mechanism of cell-division, and the principles of genetics Viruses and bacteria are introduced as examples of unicellular organisms and their ecology and place in evolution described The growth of cells in tissue culture is studied (practically also) and the factors controlling it The behavioural ideas of maturation versus learning are introduced in an elementary way even at this stage, and the behaviour of unicellular organisms and of cells such as leucocytes is shown, largely through cine films

DIURETIC ACTION OF CHLOROTHIAZIDE

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IT has been claimed that oral chlorothiazide (6-chloro-7-sulphamyl-1, 2, 4, benzothiadiazine-1, 1-dioxide), synthesised by Novello and Sprague (1957), is effective in the treatment of certain types of œdema Bayliss et al (1958) have used it successfully in congestive heart-failure and premenstrual œdema, Slater and Nabarro (1958) in œdema due to the nephrotic syndrome (3 cases) and œdema due to hepatic fibrosis with portal hypertension (1 case)

The chemical structure of chlorothiazide suggests that it acts by inhibiting carbonic anhydrase, and Beyer et al (1957) have shown that in vitro it is, in this respect, some thirty times more potent than acetazolamide ('Diamox') Slater and Nabarro (1958) have tried to assess the effect of chlorothiazide as a carbonic-anhydrase inhibitor in vivo by giving 3000 mg orally to a patient with rheumatic heart-disease and essential hypertension

Despite fairly extensive investigations on dogs (Beyer et al 1957, Ford et al 1957) and on patients with incipient heart-failure (Ford et al. 1957) there is no information about the effect of chlorothiazide on the urine and the excretion of electrolytes in healthy people The present investigation was an attempt to supply some of the essential basic information which cannot be deduced either from experiments on animals or from clinical trials Consequently we sought to determine the effect of chlorothiazide on the composition and flow of urine in healthy adult males, to assess its action in vivo as a carbonic-anhydrase inhibitor, and to compare its effect with that of acetazolamide

Methods

Investigations were made on 10 healthy males, aged 16–40, permitted normal activity and diet The intake of sodium and potassium was not accurately standardised, but on the days of experiment the intakes of food and fluid were qualitatively and quantitatively similar

Each man was studied during a control period of twenty-four hours His bladder was emptied at 9 A M, and his urine was collected under mineral oil in two-hour fractions for twelve hours The urine passed during the subsequent twelve to twenty-four hours by 5 men was collected with similar precautions and pooled The volume and pH of each sample were determined, and the urinary content of bicarbonate, chloride, phosphate, titratable acid, ammonia, sodium, and potassium during each period was measured

On a subsequent day at 9 A M each man received chlorothiazide 2000 mg by mouth, and the observations on the flow and composition of the urine were repeated The experiment was repeated on 3 men under similar conditions but with acetazolamide 500 mg instead of chlorothiazide When this was done, at least a week was allowed to elapse between the administration of the drugs to allow fluid and electrolyte balance to return to normal

The action of intravenous chlorothiazide 500 mg was also studied by collecting samples of blood before and at half-hour intervals for four hours after the administration of chlorothiazide. The hæmatocrit, plasma-carbon dioxide, plasma-chloride, serum-sodium, and serum-potassium were estimated in each sample Strict anaerobic precautions were observed in collecting the plasma for estimating carbon dioxide and chloride. Urine was collected and analysed, as in the previous experiment, before and each hour for four hours after the administration of chlorothiazide

Chemical Methods

Sodium and potassium were estimated by flame photometry, urinary chloride by modified Volhard-Harvey titration (Peters and Van Slyke 1932), plasma-chloride by the open Carius method as applied by Van Slyke, Sendroy, and Eisenman (Peters and Van Slyke 1932), carbon dioxide in plasma and urine by manometric methods, and urine bicarbonate from the ordinate of the carbonic acid-bicarbonate curve according to pH (Peters and Van Slyke 1932) Urine pH was estimated with the glass electrode, ammonia by

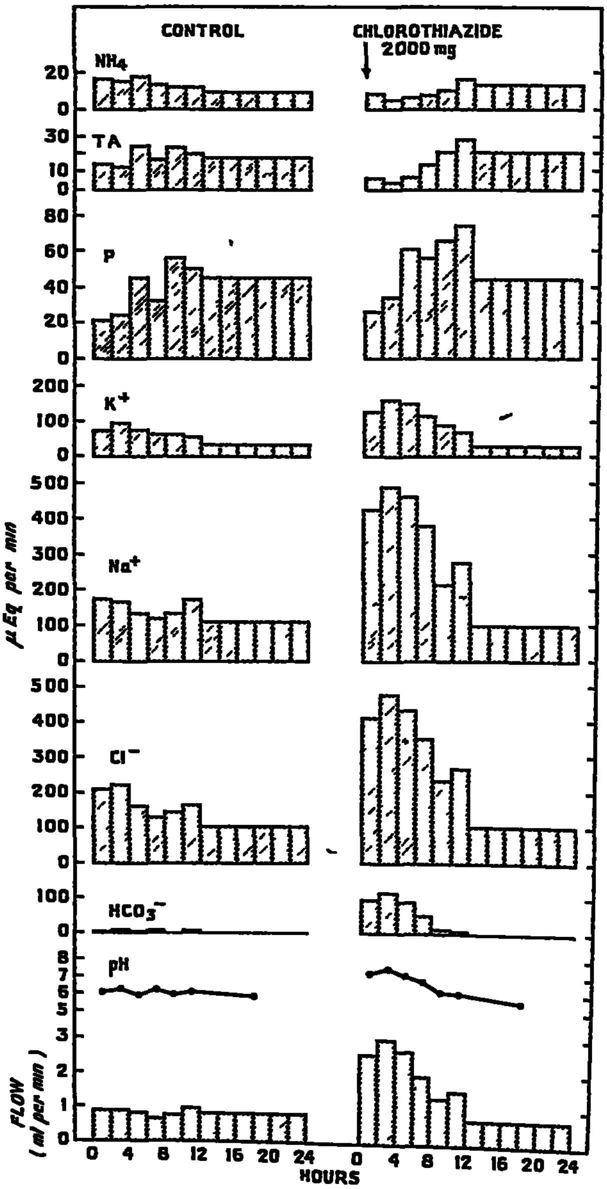

Fig 1—Average rates of excretion of water and electrolytes in 10 men after oral dose of chlorothiazide 2000 mg compared with rates of excretion during control period Note increase in excretion of sodium and chloride

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TABLE I—EXCRETION OF WATER AND ELECTROLYTES AFTER ADMINISTRATION OF CHLOROTHIAZIDE 2000 MG
Average of 10 cases

Hours after dose	Flow (ml per min)		pH		μEq per min													
					HCO_3^-		Cl^-		P		Titratable acid		NH_4^+		Na^+		K^+	
	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I
0–2	0 91	1 62	6 1	1 1	4	89	209	205	22	5	14	−8	16	−8	175	255	75	53
2–4	0 91	2 06	6 2	1 3	5	110	224	257	25	10	13	−9	15	−10	166	330	96	65
4–6	0 85	1 81	5 9	1 3	3	88	161	274	46	16	24	−17	17	−11	133	334	76	75
6–8	0 68	1 29	6 2	0 6	5	45	130	225	33	24	17	−3	13	−6	119	264	63	52
8–10	0 75	0 59	5 9	0 3	1	10	147	88	57	10	23	−2	12	−2	132	84	63	26
10–12	0 95	0 58	6 1	0	7	1	165	105	51	24	20	8	12	4	175	103	58	13
12–24	0 78	−0 04	5 8	−0 2	1	0	105	2	46	1	18	3	9	4	107	−10	32	−

C, control I, increase after administration of drug

aeration titration, titratable acidity by the method of Henderson and Palmer (1914), and inorganic phosphate by the method of Fiske and Subbarow (1925)

Results

ORAL CHLOROTHIAZIDE

In the healthy men chlorothiazide 2000 mg had a pronounced diuretic effect associated with characteristic and constant changes in the excretion of electrolytes Fig 1 compares the average rates of excretion of urine and electrolytes for 10 men after the administration of chlorothiazide with those during the control day The changes in the rates of excretion of the various electrolytes after the administration of chlorothiazide are also compared with those during the control day Table I shows these results

TABLE II—AVERAGE EXCRETION OF URINE AND ELECTROLYTES OVER FIRST SIX HOURS

—		Control	After dose	Change due to chlorothiazide	S E of change
Flow (ml per min)		0 89	2 72	−1 83	0 195
pH		6 1	7 38	+1 28	0 195
μEq per min	HCO_3^-	4	99 5	+95 5	11 30
	Cl^-	198	443 0	+245 0	34 40
	P	31	41 3	+10 3	2 51
	T A	17	5 6	−11 4	2 08
	NH_4^+	16	6 5	−9 5	3 03
	Na^+	158	464 3	+306 3	32 30
	K^+	82	146 8	+64 8	10 06

T A, titratable acid

Duration of Action

The diuretic effect appeared within two hours of oral administration, was well maintained over the first eight hours, and thereafter subsided but was not quite complete by twelve hours During the second twelve-hour period the excretion-rates returned to control values The form of the effect was the same for all measurements, rising to a maximum at about four hours (except for inorganic phosphate, whose maximum was reached somewhat later)

Table II shows the average increases over the first six hours after administration, the period of maximal action The standard errors of these figures are also given All changes of rates are considerable, even the smallest is such as to appear less than once in twenty times by chance if the chlorothiazide had had no effect

Formation of Urine

Over the first twelve hours the average output of urine was 2 6 times as great as during the control period, and almost a litre of excess urine was excreted in the twenty-four hours following the administration of chlorothiazide

Excretion of Sodium

The average excretion of sodium for twelve hours after the administration of chlorothiazide was 2 5 times that of the control and was increased 3 5 times during the maximal diuresis The average output of sodium over twenty-four hours after the administration of chlorothiazide was 342 mEq compared with 185 mEq during the control day

Excretion of Potassium

Chlorothiazide augmented the excretion of potassium to a lesser extent, the average loss over twelve hours being 1 6 times as great as the control The average output in twenty-four hours was 107 mEq after the administration of chlorothiazide compared with a control value of 75 mEq

Excretion of Hydrogen Ions and Bicarbonate

The rate of excretion of hydrogen ions, estimated from the titratable acidity and ammonium content of the urine, fell initially to about a third of the control rate (fig 1) Simultaneously the pH of the urine increased, and the excretion of bicarbonate increased to an average maximal rate which was 30 times the control rate These changes

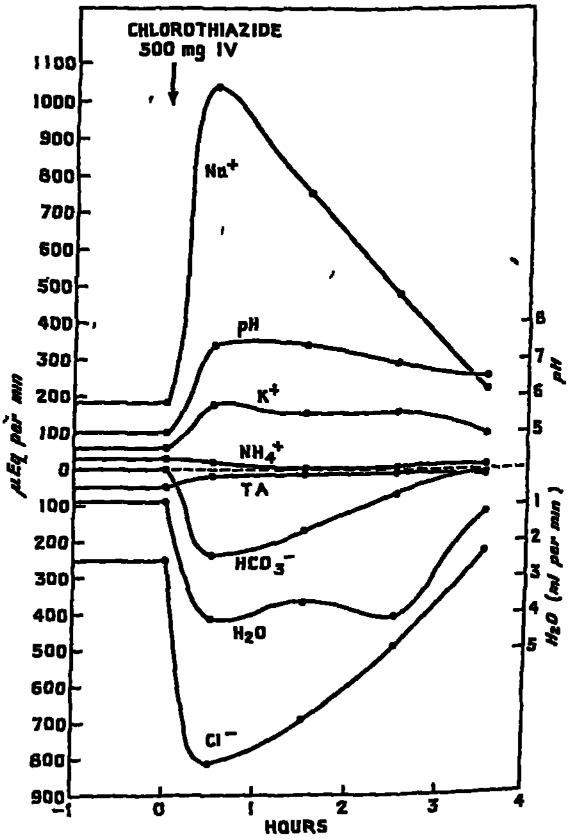

Fig 2—Pattern of excretion of electrolytes after intravenous dose of sodium chlorothiazide 500 mg

were maximal over the first six hours and complete by ten hours Thereafter the excretion-rate of hydrogen ions rose above the control rates as acid-base balance was restored

Excretion of Chloride

Chlorothiazide produced a striking increase in the excretion of chloride, approaching that of sodium Over twelve hours the rate of output was more than twice the control, and about 140 mEq was lost in twenty-four hours

Excretion of Inorganic Phosphate

The excretion of inorganic phosphate was also increased significantly throughout the period of diuresis The effect on the excretion-rate of this ion was not dramatic, and the maximal increase occurred later than in the case of other electrolytes

INTRAVENOUS CHLOROTHIAZIDE

The patterns of urinary excretion following the intravenous injection of 500 mg of the sodium salt of chlorothiazide are shown in fig 2 The changes were maximal within the first hour, and the effect lasted about four hours

The initial response was greater than that produced by oral chlorothiazide 2000 mg, but lasted a much shorter time, the loss of water, sodium, potassium, chloride, and bicarbonate being about two-thirds of the average loss following the oral administration of chlorothiazide

No change was found in hæmatocrit, plasma-carbon dioxide, plasma-chloride, serum-sodium, and serum-potassium levels during the four hours' observation

COMPARISON WITH ACETAZOLAMIDE

3 men whose response to chlorothiazide 2000 mg had been observed, were given oral acetazolamide 500 mg after an interval for recovery from the administration of the chlorothiazide The results are summarised in fig 3, where the average rates of excretion of urine and electrolytes after each drug are compared with the average rates during the control day

Chlorothiazide produced its maximal effect more rapidly than did acetazolamide, and its action lasted a shorter time In the second twelve-hour period following the administration of acetazolamide the flow and the pH of the urine and the excretion-rates of potassium, hydrogen ions, and bicarbonate had not returned to control values, whereas the action of chlorothiazide was almost complete by twelve hours

Over twenty-four hours acetazolamide produced a greater volume of urine, but more sodium was excreted after the administration of chlorothiazide The urinary excretion of potassium after the administration of acetazolamide exceeded the average control excretion by 70–80 mEq compared with 25–35 mEq after the administration of chlorothiazide Fig 3 brings out the important difference between the action of the two drugs on the urinary excretion of chloride, which was greatly increased during chlorothiazide diuresis but unaltered after the administration of acetazolamide, which caused a more striking and persistent increase in the pH of the urine and in the urinary excretion of bicarbonate and a greater decrease in the urinary excretion of hydrogen ions (fig 3)

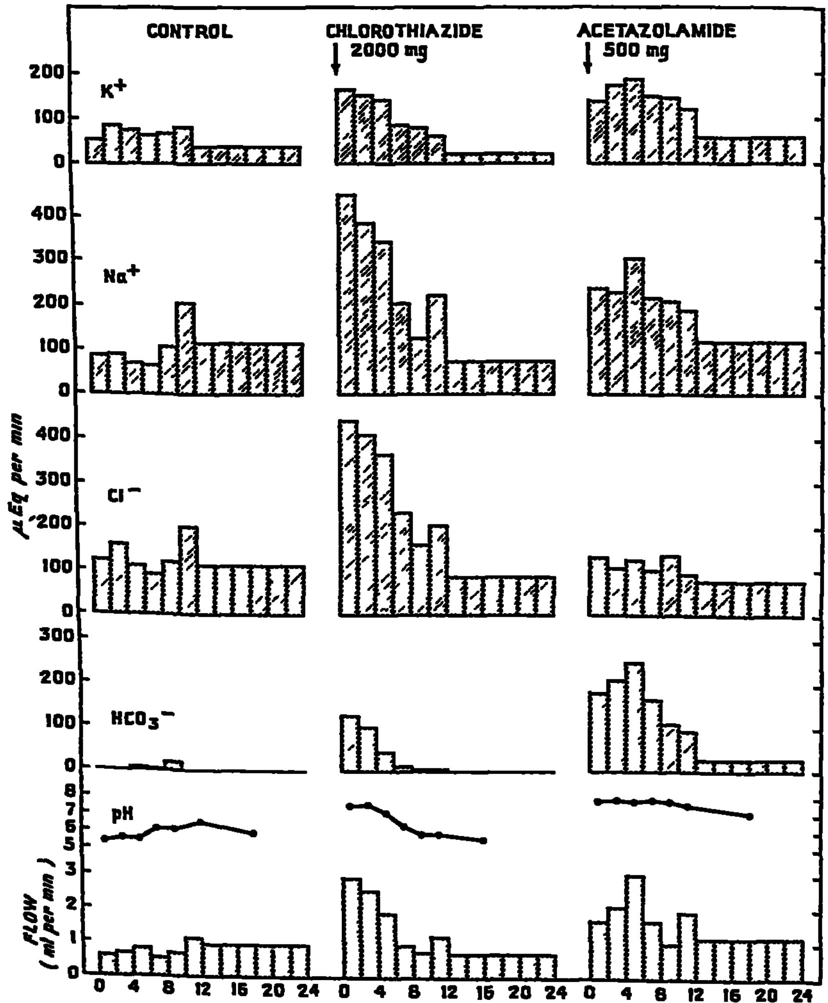

Fig 3—Average rates of excretion of water and electrolytes during control day, after oral dose of chlorothiazide 2000 mg., and after oral intravenous dose of acetazolamide 500 mg in same 3 men.

BASE ECONOMY

The difference between chlorothiazide and acetazolamide as regards the urinary excretion of hydrogen ions and bicarbonate is shown by the base economy after the administration of both drugs

The term "base economy" denotes the conservation of body base by the excretion of acid radicals, in excess of base, in the urine (Gamble et al 1923, Gamble 1949)

This is accomplished by the excretion of weakly acid components in urine, whose pH is so much lower than that of plasma that they can exist relatively base-free, and by the excretion of radicals of strong acids as ammonium salts The titration of urine to the pH of plasma gives an estimation of the free acid, and this together with the ammonium content is a measure of base

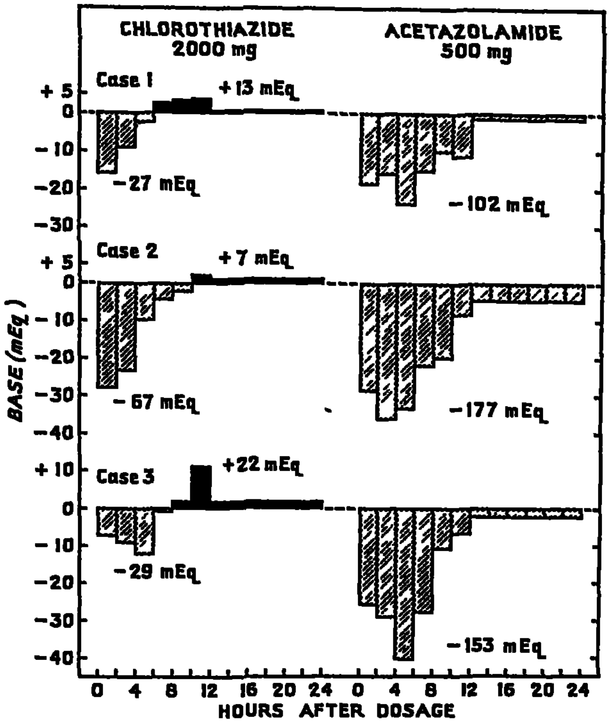

Fig 4—Comparison of depletion and recovery of base after single doses of chlorothiazide 2000 mg and acetazolamide 500 mg in 3 men Histograms below line represent loss of base, histograms above line indicate conservation of base and thus represent beginning of restoration of acid-base balance Note short-lived and relatively slight base deficit after dose of chlorothiazide

conserved Carbonic acid, normally excreted base-free by the lungs, may in certain circumstances pass into the urine as bicarbonate combined with fixed base and thus represent depletion of the alkali reserve Therefore, if urine bicarbonate is subtracted from the sum of titratable acid and ammonium content, the resulting figure, expressed in mEq , is a measure of base economy

The base economy following the administration of chlorothiazide may be calculated for any given period, if the value for the same period during the control day is subtracted from this figure, the result will represent loss or gain of base caused by the chlorothiazide (Maren et al 1954) Fig 4 compares the base deficit produced by chlorothiazide with that produed by acetazolamide Columns below the line represent loss of base, and columns above the line indicate conservation in excess of control values and thus the restoration of normal alkali reserve

This figure shows that chlorothiazide caused, in these 3 men, a total depletion of 27–67 mEq of base, and that recovery began in eight to ten hours or earlier Acetazolamide, on the other hand, produced a depletion of 102–177 mEq of base, and no recovery was evident within twenty-four hours

Discussion

In the renal tubule cells carbonic anhydrase catalyses the combination of carbon dioxide and water to form carbonic acid, which ionises to liberate hydrogen ions These ions pass into the tubular urine in exchange for sodium and combine with bicarbonate to facilitate its reabsorption as carbon dioxide and water The physiological function of the enzyme is thus the conservation of base by promoting reabsorption of sodium and bicarbonate, by increasing the excretion of hydrogen ions and by lowering the pH of the urine Further, it is believed that a competitive mechanism exists between potassium and hydrogen for tubular transport (Berliner et al 1950) Accordingly carbonic anhydrase must limit the tubular secretion of potassium A carbonic-anhydrase inhibitor, by preventing these processes, greatly increases the excretion of bicarbonate, moderately increases the excretion of water, sodium, and potassium, increases the pH of the urine, and decreases the excretion of hydrogen ions The action of acetazolamide in inhibiting the enzyme is well known (Friedberg et al 1952, Counihan et al 1954)

The observation that chlorothiazide inhibits carbonic anhydrase in vitro, together with the characteristic changes which it causes in the excretion of water, bicarbonate, sodium, and potassium, suggests that carbonic anhydrase inhibition plays a part in the action of chlorothiazide, but the pattern of excretion of electrolytes after the administration of chlorothiazide is sufficiently different from that seen after the administration of acetazolamide to make it certain that there is an additional action

The increase in excretion of sodium and chloride in about equimolar amounts is a characteristic feature of chlorothiazide diuresis It is likely that the therapeutic value of chlorothiazide will depend on this latter property

The urinary excretion of inorganic phosphate was increased after the administration of chlorothiazide This does not happen in osmotic diuresis (Havard and Reay 1926, Mudge et al 1949) Although increased excretion of phosphate is assocated with acidosis (Harrison and Harrison 1941, Pitts and Alexander 1944), it is unlikely that this will explain the increase after the administration of chlorothiazide, because acidosis must be minimal after a single dose of this drug

From comparison of the effects of chlorothiazide and acetazolamide on the urinary excretion of bicarbonate and hydrogen ions it seems reasonable to deduce that chlorothiazide is less potent than acetazolamide as a carbonic-anhydrase inhibitor in vivo Consequently the acid-base balance is rapidly restored after the administration of chlorothiazide (fig 4) Acetazolamide in repeated doses has a self-limiting effect because systemic acidosis and decreased glomerular filtration of bicarbonate result from its action (Nadell 1953, Counihan et al 1954, Hanley and Platts 1956), but chlorothiazide has a sustained effect (Ford et al 1957), and this difference is explained partly by the rapid restoration of the acid-base balance and partly by the action of chlorothiazide on the excretion of sodium and chloride, to which most of its diuretic effect is due

Chlorothiazide tends, especially during prolonged administration, to produce hypopotassæmia (Bayliss et al 1958, Slater and Nabarro 1958) In our experiments using single doses the excretion of water and potassium was greater with acetazolamide than with chlorothiazide, but, since the effect of chlorothiazide is unlikely to be interrupted by acidosis, repeated doses of it will lead to a greater loss of water and potassium

Summary

In healthy men oral chlorothiazide 2000 mg is an effective diuretic The action begins within two hours of administration and lasts for at least twelve hours

Chlorothiazide causes a pronounced increase in the urinary excretion of sodium, chloride, and water, an increase in that of bicarbonate, potassium, and phosphate, and a decrease in that of hydrogen ions

The action of chlorothiazide may be due in part to carbonic-anhydrase inhibition, but its striking effect on

the urinary excretion of chloride suggests that another mechanism is involved

Compared with acetazolamide 500 mg, chlorothiazide 2000 mg is a less potent carbonic-anhydrase inhibitor, hence recovery of base is more rapid

The action of chlorothiazide is likely to be maintained and, because of this, may induce hypopotassæmia

We wish to thank Dr D Finney and Mr R Cormack for statistical analysis and suggestions about the presentation of the tables, Dr J J E Merry, of Messrs Merck, Sharp and Dohme, Ltd, for a generous supply of chlorothiazide ('Saluric'), and the volunteers who took part in the experiment

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CLINICAL AND LABORATORY STUDIES WITH CHLOROTHIAZIDE: AN ORAL DIURETIC

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CHLOROTHIAZIDE, a benzothiadiazine derivative, is a non-mercurial diuretic which has been reported to be effective and safe on oral administration (Bayliss et al 1958, Slater and Nabarro 1958, Ford et al 1958) Further investigation is necessary before its pharmacological action is fully understood, especially on its effect on the passage of electrolytes through the kidney

We have investigated the nature and degree of diuresis obtained with chlorothiazide in various clinical states associated with retention of fluid Twenty-six "acute" experiments were performed on 22 patients with the following clinical conditions

Congestive heart failure	9
Cor pulmonale with cardiac oedema	3
Pre-eclamptic toxæmia of pregnancy	3
Chronic azotæmic uræmia	1
Nephrosis	1
Hypertension	2
Hepatic cirrhosis with ascites and oedema	1
Fulminating bronchiolitis and acute congestive heart-failure	1
Steroid oedema	1
Total	22

Method

By an "acute" experiment we mean a study on the effect of a single oral dose of chlorothiazide 2 g

The patient's urine was collected for twenty-four hours up to 9 A M on the day of the test At 9 A M he was given chlorothiazide 2 g, and the next twenty-four hours' excretion of urine was collected in two amounts—a six-hour fraction from 9 A M to 3 P M, and an eighteen-hour fraction from 3 P.M to 9 A M Each sample of urine was measured, its pH recorded, and its Na, Cl, and K concentration estimated Samples of blood were taken at the end of each collection period and their protein, urea, Na, K, Cl, and alkali reserve were estimated Urinary bicarbonate was not measured, but it can be approximately calculated from the Na, K, and Cl values, since phosphate, the other important anion, is excreted in small and only slightly varying amounts (Ford et al 1958) Sodium and potassium were measured by flame photometry, chloride by mercuric-nitrate titration (Schales and Schales 1941), and alkali reserve by the gas volumetric method (Van Slyke and Cullen 1917) Urea was estimated by the method described by King (1951), and serum-protein by the biuret method (Gornall et al 1949), and pH of urine with narrow-range indicator paper (British Drug Houses)

Results

Table I gives the average hourly excretion-rates of urine and electrolytes (in all except the last 2 cases) for the twenty-four hours before the administration of chlorothiazide (period I), the next six hours (period II), and the subsequent eighteen hours (period III)

Clearly there is a considerable increase in the flow of urine, which is greater in the six hours immediately after the administration of chlorothiazide This is associated with an increased output of electrolytes—sodium, chloride, bicarbonate, and potassium in that order of magnitude In the main there was little alteration in the serum-electrolytes The serum-urea level was altered in only 1 patient, who had chronic nephritis after a considerable diuresis it rose from 146 to 236 mg per 100 ml

Other points of interest are most easily considered in brief analyses of the different clinical groups

Congestive Heart-failure

8 of the 9 patients conformed to the general diuretic pattern. The findings in the remaining patient are of special interest and are detailed in table II, which shows that, before the administration of chlorothiazide, she was in a state of moderately severe depletion of sodium and chloride In spite of this she had a satisfactory diuresis with only minimal excretion of electrolyte Fig 1, which should be compared with table I, shows this discrepancy more clearly The explanation of this apparent water diuresis is obscure (nor can the increase in the alkali reserve be readily explained) Possibly chlorothiazide may interfere with the action of antidiuretic hormone (A D H) or its release from the posterior lobe of the pituitary gland

Cor Pulmonale with Cardiac Œdema

Although chlorothiazide increased the output of urine in each of these 3 patients, in only 1 was there a satisfactory diuresis In this patient it was associated with an almost equal output of chloride and bicarbonate during the first six hours (15 3 and 12 2 m Eq per hour respectively) In spite of increased bicarbonate loss the alkali reserve increased from a pre-chlorothiazide level of 32 5 m Eq per 100 ml to 36 0 m.Eq per 100 ml

The generally poor diuretic response of this group cannot be attributed either to a deficiency of serum-electrolytes or to poor glomerular filtration, because the serum-urea levels were also normal Our experience with these 3 patients supports our clinical impression that special factors contribute to the mechanism of fluid retention in patients with chronic bronchitis and right heart-failure.

Pre-eclamptic Toxæmia

In all 3 patients there was a substantial diuresis during the six hours after the administration of chlorothiazide In each it was considerably greater than the series mean (201 7, 181 7,

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TABLE I—AVERAGE EXCRETION-RATES OF URINE AND ELECTROLYTES DURING THREE EXPERIMENTAL COLLECTION PERIODS

Period	Urine per hour (ml)		Na per hour (m Eq)		K per hour (m Eq)		Cl per hour (m Eq)		HCO_3 per hour (m Eq)	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range
I 9 A M –9 A M	46 6	1 8–96 5	4 92	0 07–10 90	1 28	0 06–2 43	4 45	0 03–10 00	1 66	0–8 77
II 9 A M –3 P M	140 0	43 3–273 0	22 06	1 50–63 41	3 89	0 61–11 83	16 52	1 52–39 66	8 88	0 61–46 69
III 3 P M –9 A M	79 3	39 4–131 0	9 87	1 02–43 20	1 81	1 03–3 00	9 34	1 07–39 70	2 52	0–6 78

TABLE II—URINE AND ELECTROLYTE LEVELS IN 9TH CASE OF CONGESTIVE HEART-FAILURE

Period	Serum					Urine				
	Urea (mg)	Na (m Eq)	K (m Eq)	Cl (m Eq)	HCO_3 (m Eq)	Volume (ml)	Na (m Eq)	K (m Eq)	Cl (m Eq)	pH
I	27	116	4 8	90	23	440	4	22 8	22	5 9
II	28	116	4 4	87	28	740	15	22 0	37	5 9
III	23	116	4 7	85	36	1850	24	24 0	52	—
										HCO_3 (m Eq)
I	Hourly excretion-rate					18 4	0 07	0 42	0 40	0 09
II						123 3	1 85	2 70	1 52	3 02
III						102 6	2 47	2 47	5 15	0

and 201 7 ml an hour) It decreased rapidly to average values during the next eighteen hours In 2 patients the electrolyte excretion conformed to the usual pattern, but in the 3rd patient the excretion of K and HCO_3 was greater than average during the period of maximum diuresis (17 00 and 12 23 m Eq per hour respectively) No significant fall in blood-pressure was noticed during or immediately after the acute experiment

Renal Disease

We performed 3 acute experiments on a patient with nephrosis The pattern of urinary excretion of electrolytes was roughly the same in each During the first study, however, the urinary excretion of Na and HCO_3 increased to the very high values of 63 41 and 46 69 m Eq per hour respectively This was the only occasion on which we observed side-effects—namely, marked weakness Though this seems to have been due to the massive loss of sodium rather than potassium, the levels of these ions in the serum altered little and remained within normal limits (Na 134 m Eq per 100 ml each time, K 3 9–4 6 m Eq per 100 ml)

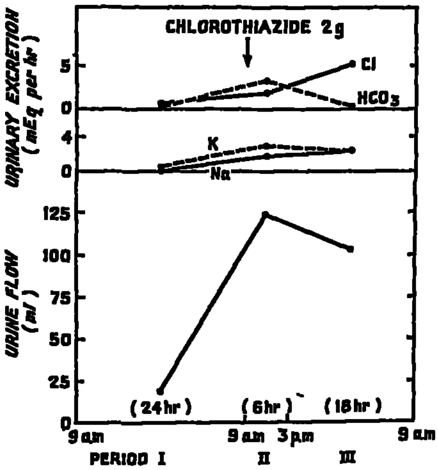

Fig 1—Congestive heart-failure, showing substantial diuresis associated with very low excretion of electrolytes

We studied 1 case of chronic nephritis in the terminal phase Although the patient was severely acidotic (alkali reserve 18 m Eq per 100 ml), the substantial diuresis which occurred was associated with a considerable output of HCO_3, with the result that the alkali reserve decreased to 14 m Eq per 100 ml by the end of period II Then, in spite of continuing excretion of bicarbonate, the alkali reserve increased to 21 m Eq per 100 ml by the end of period III This was the only patient in whom the serum-urea level rose (from 146 to 236 mg per 100 ml)

Hypertension

2 cases were studied A woman with no evidence of œdema, heart-failure, or renal disease, obtained an excellent diuresis (227 5 and 111 5 ml per hour during periods II and III respectively) associated with the usual pattern of excretion of electrolytes The other patient, who had left heart-failure with pulmonary congestion, albuminuria, and moderate uræmia (blood-urea 110 mg per 100 ml) gave no response She was hypochloræmic (88 m Eq per 100 ml), but the other serum electrolyte levels were normal Poor glomerular filtration may have been the adverse factor here

Hepatic Cirrhosis

After the first dose of chlorothiazide this patient had a diuresis of 3 5 litres in twenty-four hours, and the abdominal girth at the umbilicus decreased by 2 inches The detailed experimental results of the second dose given a week later are shown in fig 2 There are two features of interest (1) a good diuresis during period II without a corresponding increase in the excretion of electrolytes, and (2) a sustained diuresis during period III associated with considerably increased excretion of sodium and chloride The following explanations for this unusual type of response seem worthy of consideration the diuresis in period II may be another example of mainly "water diuresis", while the prolonged augmented response in period III may reflect delayed absorption or impaired metabolism of chlorothiazide due to the underlying liver disease

Although serum-potassium levels were low (3 2–3 5 m Eq per 100 ml), no symptoms of hypokalæmia arose, and it is noteworthy that potassium excretion was negligible

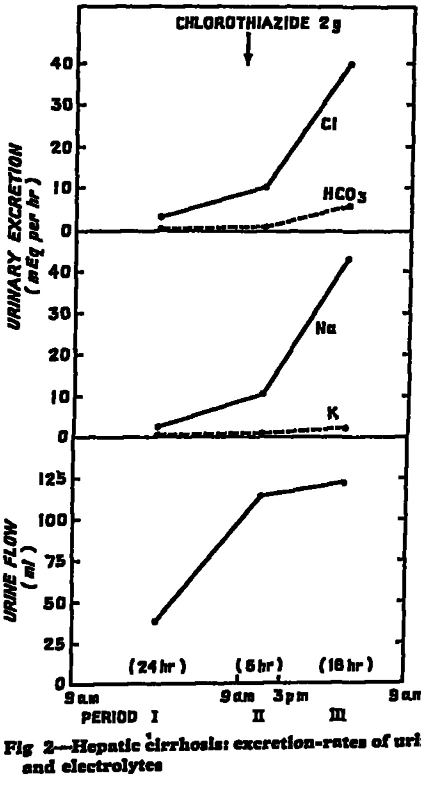

Fig 2—Hepatic cirrhosis: excretion-rates of urine and electrolytes

Steroid Œdema

This patient, in the sixth month of pregnancy and receiving cortisone 150 mg daily to prevent erythroblastosis fœtalis, developed puffiness of her face Chlorothiazide produced a diuresis of 3 37 litres in twenty-four hours with a proportionate loss of all electrolytes, there was no significant change in the serum-electrolyte levels

Bronchiolitis and Heart-failure

The last case was a young man, with acute fulminating bronchiolitis and toxic myocarditis, in a state of hypochloræmic alkalosis (Cl 84 m Eq per 100 ml , alkali reserve 40 m Eq per 100 ml) In period II the volume of urine was 83 3 ml per hour, compared with 7 6 ml per hour in period I This moderate diuresis was associated with minimal excretion of Na and Cl (1 67 and 2 00 m Eq per hour respectively) and proportionately greater excretion of K and HCO_3 (6 33 and 6·00 m Eq per hour respectively) During period III the patient became incontinent and further study of his urine was impossible

Discussion

The diuresis which occurs after the administration of chlorothiazide is associated chiefly with an increased excretion of sodium and chloride When the serum levels of these electrolytes are low, the drug will not compel their excretion in such circumstances it tends to promote the excretion of potassium and bicarbonate Hypochloræmia can easily be corrected, however, by administering ammonium chloride, and this simple expedient might augment the diuretic action of chlorothiazide in such patients as it augments the action of mersalyl

In 2 of our cases a significant amount of bicarbonate was lost in the presence of a low alkali reserve In 3 others moderate loss of bicarbonate was associated with an increasing alkali reserve We have seen a satisfactory diuresis in the absence of a corresponding electrolyte loss and we wonder if this denotes an anti-A D H activity of chlorothiazide

In general the best diuretic response occurred in the type of patient who responds well to mersalyl In patients with pulmonary heart-disease the response was disappointing After six months' experience with chlorothiazide we are not certain that tolerance develops, nor are we convinced that a regimen of divided doses (i e , 1 0 g b d) has any clinical advantages We feel that, unless there are urgent reasons for obtaining a maximal diuresis, single doses are preferable because they avoid the fatigue of unnecessary nocturia

Summary

The clinical and biochemical effects of a single dose of chlorothiazide 2 g given to each of 22 patients with various " water-retaining " conditions are reported

Chlorothiazide is an effective and safe oral diuretic which acts principally by promoting excretion of sodium and chloride but in certain circumstances by promoting excretion of potassium and bicarbonate Occasionally it may produce a water diuresis

Certain practical aspects of its use are discussed

Chlorothiazide was supplied by Messrs Merck, Sharp, and Dohme

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THE DEVELOPMENT OF THE NIPPLE IN PREGNANCY

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IT is widely believed that many women have nipples which require active treatment during pregnancy to make them suitable for breast-feeding

This opinion was first made popular by Waller (1939), who subsequently described a test for the detection of defective nipples " In imitation of the action of the baby's jaws the areola is pinched [by the thumb and forefinger] just beyond the nipple's base ", if the nipple projects when this is done it is considered to be " protractile " and therefore satisfactory (Waller 1946)

Of 200 primigravidæ examined by Waller 56 had " poor protraction ", 95 " moderate protraction ", and only 49 " good protraction "

On a similar basis Blaikley et al (1953) thought that 52 of 234 primigravidæ had nipples which required antenatal treatment because they were "poorly protractile", and Naish (1948) stated that " retracted nipples and nipples poorly formed are a common abnormality " requiring treatment early in pregnancy

Manual expression of colostrum, manipulation of the nipple, and the wearing of nipple shields during the last three months of pregnancy are claimed by both Waller and by Blaikley et al to give excellent results

A defective nipple, from the functional point of view, is one which hinders suckling, and on this basis the incidence of poor nipples is very much smaller than when they are arbitrarily assessed in early pregnancy

In Aberdeen, for example, where there is seldom any antenatal treatment of the nipples, only 4 3% of 2461 first babies had any difficulty in fixing owing to poor nipples, and only 2 5% had to be weaned for this reason (Hytten 1954)

Spence (1938) also considered poor nipples to be a minor cause of feeding difficulty

This suggests either that the clinical assessment of nipples early in pregnancy is unreliable or that many " poor " nipples improve spontaneously during pregnancy Clearly the value of antenatal treatment of the nipples could only be assessed if a matched control group receiving no treatment were studied at the same time

Some doubt has been cast on the value of preparing the breasts during pregnancy

Stone (1946) says " Preparation for the act of nursing begins during pregnancy chiefly by avoiding most of the local manipulations and applications which are so widely and indiscriminately advocated "

The Ministry of Health (1943) goes further, discussing why some women dislike breast-feeding " In some cases this distaste may have been engendered by an unnecessarily elaborate routine prescribed during the antenatal period. It is, we fear, bordering on the paradoxical to impress upon the ordinary expectant mother that breast feeding is a normal, easy and natural process, if at the same time the advice she receives as a routine imposes on her the need for an elaborate daily ritual of preparation We think it possible that with an anxious type of woman too much insistence on preparation of the breasts may alarm and discourage her to such an extent that she will refuse to initiate breast feeding "

Cummane (1938) made the same point.

The present investigation was planned to assess the changes which take place in the nipple during pregnancy,

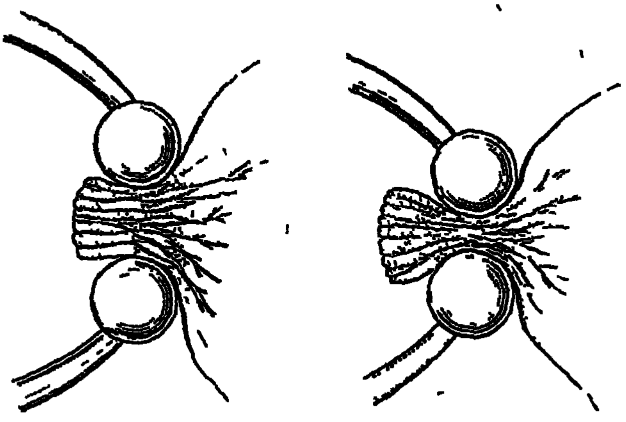

Fig 1—Measurement of " bite ", showing how tissue behind nipple is compressed

and to define more accurately the incidence of unsatisfactory nipples

Material and Methods

Material—Clinical assessments and measurements of the nipple and areola (see below) were made in 170 primigravidæ and 104 multigravidæ at their first visit to the antenatal clinic between the 8th and 15th weeks of pregnancy, and repeated at subsequent visits to the clinic and on the 1st postpartum day Only women booking at the clinic later than the 15th week of pregnancy were excluded, there was no other conscious selection All measurements and assessments were made by one staff midwife No antenatal preparation or treatment of nipples was undertaken

Methods of Assessment—" Protractility " was estimated by pinching the areola between the thumb and forefinger in the manner described by Waller (1946) An attempt was also made to assess the ability of the nipples to become erect, but the response seemed to depend to a large extent on factors such as air temperature and could not be reliably elicited by manipulation After clinical examination three measurements were made (1) the diameter of the areola, (2) the diameter of the nipple, and (3) the " bite "—the minimal thickness of tissue behind the nipple The last was measured by compressing the areola immediately behind the nipple in the position where the baby makes its grip for suckling, with ¼-inch diameter ball-ended callipers to a point just short of discomfort for the mother * (fig 1)

Follow-up—The breast-feeding performance of each woman was closely observed in hospital, and difficulties were noted in detail

Clinical Findings

Of the 170 primigravidæ whose nipples were tested by Waller's method 59 (34 7%) showed at least some evidence of poor protraction in early pregnancy, the incidence was not related to maternal age Gradual improvement took place during pregnancy, and by the puerperium the number was reduced to 13 (7 7%), however, the nipples of 1 woman were protractile in early pregnancy but deteriorated progressively and became retractile by the puerperium

Of the 170 primigravidæ 11 experienced difficulty in feeding, wholly or partly owing to the inability of the baby to fix to the nipples, and 7 of them had to abandon breast-feeding 6 of these were from the 13 women whose nipples remained poorly protractile throughout pregnancy (3 gave up breast-feeding), a 7th was the woman whose nipples deteriorated during pregnancy, and the remaining 4 had normally protractile nipples

Thus, of the 59 women who showed poor protraction in early pregnancy about 10% eventually had difficulty in suckling, and 5% abandoned breast-feeding at least partly for this reason, of the 111 other women whose nipples were clinically normal in early pregnancy about 4 5% had difficulty and about 3 5% gave up for this reason

Of 75 women with second babies only 8 (10 5%) had poorly protractile nipples in early pregnancy, in 3 this persisted after delivery, and in 2 of them there was difficulty in fixing None of 29 women with a third or later child had poor nipples or difficulty in fixing

It was seldom possible to predict which nipples would cause difficulty in feeding, because success or failure in suckling depends very largely on the efficiency of the baby For example, in 3 instances where the nipples were protractile but smaller than average there was considerable difficulty because the baby was lethargic, on the other hand, in several cases nipples which by Waller's definition would be classified as poor caused no difficulty, because the baby sucked vigorously

Measurements

Diameter of Areola

The diameter of the areola increased progressively throughout pregnancy For primigravidæ the mean increase from 34 mm in early pregnancy to 50 mm in the early puerperium was approximately linear, but some records showed irregularity because of such influences as contraction of the areola owing to cold Multigravidæ showed a similar increase from about 36 mm to 52 mm

For primigravidæ the average increase in the diameter of the areola was less as maternal age increased (table I), but there was no age gradient for multigravidæ

Diameter of Nipple

The diameter of the nipple cannot be measured exactly, because it varies with the degree of erection There is no doubt, however, that the diameter increases during pregnancy from a mean of about 9 5 mm to 11 5 mm in primigravidæ and from about 10 mm to 12 5 mm in multigravidæ There are no obvious differences due to age

" Bite "

The measurement of " bite " may be regarded as a quantitative assessment of the protractility of the nipple because, in the case of a nipple which will not pull forward, the calliper ends cannot be approximated and will therefore register a large " bite ", conversely, the nipple which is easily mobile has loose readily-compressed tissue behind it and therefore a small " bite " Table II shows the relationship between the clinical assessment of protraction and the " bite " at the first antenatal visit Almost

TABLE I—EFFECT OF AGE IN PRIMIGRAVIDÆ ON INCREASE OF AREOLAR DIAMETER DURING PREGNANCY

Maternal age (yr)	No of subjects	Mean diameter of areola (mm) 8–15 wk of pregnancy	Early puerperium	Increase %
15–19	14	35 8	58 4	63
20–24	90	34 0	51 6	52
25–29	48	34 0	48 5	43
30+	18	33 0	44 2	34

The decreasing response with increasing age is statistically significant

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* Spring-loaded callipers were used in the early stages of the experiment in an attempt to ensure complete objectivity of measurement, but no single spring pressure was universally suitable—for example, a very powerful spring was needed in some women to give the degree of compression comfortably obtained by the hand callipers, and this pressure caused pain to other women

TABLE II—RELATIONSHIP BETWEEN CLINICAL ASSESSMENT OF NIPPLE PROTRACTION AND SIZE OF "BITE" IN 170 PRIMIGRAVIDÆ IN EARLY PREGNANCY

—	Bite' (mm)				
	1–2	3–4	5–6	7–8	9–10
No of subjects	11	56	71	30	2
No having poorly protractile nipples	0	0	32 (*45%*)	25 (*83%*)	2 (*100%*)

all nipples which had a "bite" of more than 6 mm were considered clinically to be unsatisfactory, when the "bite" was 6 mm, about half the nipples were poorly protractile, and all nipples with a "bite" of 4 mm or less were clinically satisfactory

Usually the "bite" decreased during pregnancy Fig 2 shows the change in the distribution of the measurement between early pregnancy and the puerperium for the 170 primigravidæ In early pregnancy about 40% had measurements of 4 mm or less, by the puerperium this proportion had risen to almost 80%

Of the 103 (about 60%) who had a "bite" exceeding 4 mm in early pregnancy, in 83 the "bite" had decreased to 4 mm. or less at delivery, and 6 others, in which the "bite" was initially small, showed an increase to 6 mm or more Of these 26 women in whom the postpartum "bite" of the nipples measured 6 mm or more 9 had difficulty in feeding because of inability to fix, of the 144 women in whom the postpartum "bite" was less than 6 mm there was difficulty in fixing in 4

In multigravidæ the mean "bite" was initially much smaller than for primigravidæ, and the improvement during pregnancy was less striking The proportion with a "bite" of 4 mm or less was about 70% in early pregnancy and increased to 83% in the puerperium Of the 104 multigravidæ 32 had a "bite" measuring more than 4 mm in early pregnancy, and in 10 of these the "bite" was still more than 4 mm after delivery, they caused difficulty in feeding in only 1 case In 5 others the "bite" increased from 4 mm in early pregnancy to 6 mm or more, but there was no trouble in feeding

Maternal age had no obvious effect on the measurement of the "bite"

Discussion

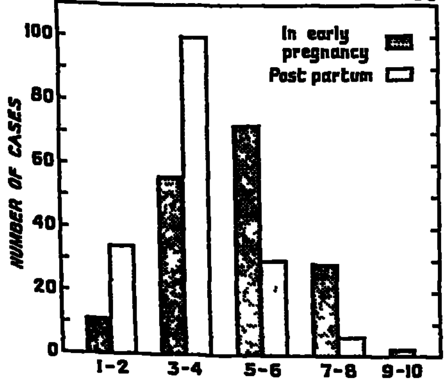

Fig 2—Distribution of size of "bite" in 170 primigravidæ in early pregnancy and postpartum

Waller's method of assessing the nipple has some predictive value because poor protraction in early pregnancy doubles the risk of difficulty in "fixing" during lactation, but it is of little value in the individual case, because 9 out of 10 women whose nipples show poor protraction early in pregnancy have no difficulty with fixing, largely because their nipples have become normally protractile by the end of pregnancy Since about a third of our primigravidæ were judged to have poorly protractile nipples in early pregnancy and Waller (1950) states that the test "reveals in rather more than a third of our patients in their first pregnancy enough defect in one or both nipples to threaten difficulty", it is reasonable to assume that our standard of assement is comparable with his Our findings are also in broad agreement with those of Blaikley et al (1953), who considered 20% of 234 primigravidæ to be in need of treatment

Waller states that at least some improvement can be expected from treatment "in all but a few", and Blaikley et al claimed "complete correction" or "good improvement" in 49 of their 52 women with poorly protractile nipples, but in neither paper was the state of the nipple at the end of pregnancy correlated directly with the actual feeding performance The fact that in our subjects just as much improvement took place in the development of all but a few nipples without treatment suggests that the changes they undergo during pregnancy, which make them more suitable for breast-feeding, are physiological and not the result of treatment

If this is so, treatment should be reserved for the small group of primigravidæ whose nipples remain poorly protractile throughout pregnancy, but there is no test which can be used early in pregnancy to differentiate them from those cases in which improvement will take place spontaneously as pregnancy progresses Such cases may constitute the small group which both Waller and Blaikley found to be resistant to treatment

The changes in the nipple brought about by pregnancy seem to be cumulative, hence a woman starts her second pregnancy with better-developed nipples than she had early in her first pregnancy After three or more pregnancies a nipple rarely gives any trouble in feeding or fails any test which might be applied to it Epidemiological studies of breast-feeding performance confirm this—for example, 4 3% of 2461 Aberdeen primiparæ experienced feeding difficulty due to unsatisfactory nipples, but only 1 7% of 3995 multiparæ had trouble of this kind, and within this group the incidence of difficulty decreased as parity increased (Hytten 1954) Clearly the influence of parity must be taken into account in assessing the effects of treatment

Naish (1948) instanced women who had been unable to breast feed their first baby because of unsatisfactory nipples but managed to feed their second babies after treatment, but improvement between first and second pregnancies is to be expected in more than half such cases even without treatment

Apart from its effect on the area of the areola, shown in table II, maternal age seems to have no important influence on the development of the nipples, and this is in keeping with the observation that the incidence of difficulty in breast-feeding due to poor nipples is uninfluenced by age (Hytten 1954) By contrast, there is a strong correlation between age and the development of the secretory breast tissue (Hytten, unpublished), the difference may be explained by the fact that the development of secretory breast tissue in pregnancy is one of growth, whereas the most important changes in the nipples are those which give it greater mobility, growth per se being relatively unimportant Increasing maternal age presumably affects this process of mobilisation much less than it affects cell proliferation

In view of the changes in the nipple which we have found during pregnancy, routine antenatal preparation of the breasts and nipples seems to be unnecessary Whether the small group of women whose nipples do not undergo the usual physiological changes would benefit from the types of local treatment usually advocated is doubtful The effectiveness of treatment could be assessed only by a closely controlled trial on a sufficient scale

Summary

The nipples of 170 primigravidæ and 104 multigravidæ were studied clinically and by measurement from early pregnancy until the puerperium No antenatal treatment was given to "defective" nipples

The nipples of about a third of the primigravidæ were judged to be defective, on grounds of retraction or poor protraction, in early pregnancy, but only about 8% were judged to have defective nipples in the puerperium In second pregnancies the proportions were 10% in early pregnancy and 4% in the puerperium In third and subsequent pregnancies none of the women examined had defective nipples These changes in the nipple were confirmed by measurement

The assessment of nipples in early pregnancy gives limited help in predicting which women will experience difficulty with breast-feeding due to inadequacy of the nipples This kind of difficulty with breast-feeding is, in any case, relatively uncommon, it affects less than 5% of primigravidæ and less than 2% of multiparæ who start breast-feeding

The value of routine "preparation" of breasts and nipples during pregnancy, with a view to improving prospects for breast-feeding, is dubious, and the anatomical improvements claimed for such treatment are probably due, in most women, to normal physiological changes during pregnancy

We are grateful to Staff Nurse C Mearns and to our colleagues in the Aberdeen Maternity Hospital and Midwifery Department of the University of Aberdeen for invaluable help with the investigation

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COMBINED GASTROSCOPY AND GASTRIC BIOPSY UNDER DIRECT VISION

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EVERY gastroscopist experiences uncertainty of the nature of the lesion which he finds For this reason attempts at biopsy of the gastric mucosa under direct vision were made by Benedict (1948), who attached biopsy forceps to Schindler's flexible gastroscope, and by Tomenius (1952) using suction biopsy with the same kind of gastroscope Both methods have their disadvantages With Benedict's forceps there is uncertainty of the depth of biopsy taken, and with Tomenius' method biopsy cannot be done under direct vision, because there is a distance of about 4 cm between the viewing lens of the gastroscope and the biopsy aperture, necessitating withdrawal of the instrument by that same amount

In an attempt to obtain better visual control of gastric biopsy and to control the thickness of the mucosal specimen Wood's gastric biopsy tube was modified to fit the Hermon Taylor gastroscope, as described by Shiner (1956), and has since been further modified, as described below We have successfully done 53 biopsies and discuss here the method of biopsy, its applications, and its difficulties

The Instrument

The instrument (fig 1) consists of the Hermon Taylor gastroscope fitted with an adjustable focusing eyepiece and carrying the modified Wood's gastric biopsy tube on its anterior surface This consists of a hollow plastic tube 62 5 cm long and 3 0 mm in diameter The biopsy head at its distal end has an oval aperture measuring 3 5 mm × 2 5 mm The position of the biopsy aperture is identified by a black cross, which is directly opposite its central point The biopsy knife is operated by scissor forceps at the proximal end, thus making it possible to open and close the biopsy aperture with one hand only A lateral exhaust at the proximal end serves for attachment of a manometer and a syringe to suck mucosa into the biopsy aperture at a known pressure The distal part of the biopsy tube runs in a tunnel formed by a hollow spiral tube covered with plastic material, the whole being attached to the gastroscope by an outer sheath 15 5 cm long The upper part of the biopsy tube is fixed to the gastroscope by two or three short rubber bands When retracted the headpiece rests on the rubber sheath of the gastroscope just below its point of emergence from the outer sheath (fig 2) The combined instrument assumes an oval shape with a diameter of 1 85 cm at its widest point

Its Application

Before introduction the instrument is thoroughly tested, particularly the up and down movement of the biopsy tube and knife, and the central position of the biopsy head in relation to the viewing lens The patient is prepared in the usual way for gastroscopy The instrument is introduced in the left lateral position with the greatest diameter in the transverse position of the pharynx and œsophagus After thorough inspection of the stomach the site of biopsy is chosen The biopsy tube is then pushed down so that the headpiece overlies the viewing lens (fig 3) It is rotated until the black cross appears in the centre of the field of vision The biopsy aperture then faces the gastric wall By flexing the gastroscope towards the site of biopsy the headpiece is approximated to the mucosa The biopsy knife is then operated with the scissor forceps to open the aperture, the manometer and syringe are fixed, and suction is applied to register a steady negative pressure of 15–20 inches *Hg* This may only be achieved by exhausting, through the syringe, some of the air previously introduced The pressure is maintained while the scissor forceps are closed, thus securing a specimen within the biopsy tube

Two or three biopsies may be obtained by this method After each biopsy the tube is withdrawn to its resting position, and the biopsy site is inspected, slight oozing can usually be seen coming from it The whole instrument is subsequently withdrawn

Results

The 67 patients subjected to this procedure were drawn mainly from outpatients One of us (P E T H), who has done more than 3000 gastroscopies, used the combined instrument on 57 patients presenting consecutively

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* In receipt of a grant from the Medical Research Council

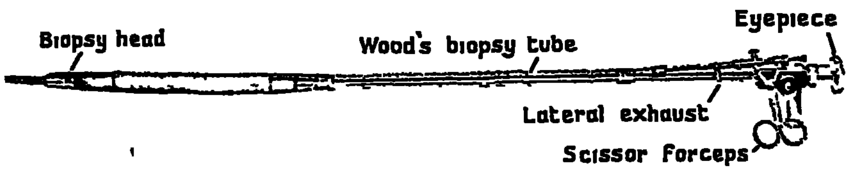

Fig 1—Combined Hermon Taylor gastroscope and biopsy instrument

for gastroscopy Neither difficulties in introduction nor complications were encountered in any of the patients, who were carefully questioned about the amount of discomfort, this was judged about equal to that experienced in ordinary gastroscopy In 6 cases the gastroscope could not be passed beyond the cardia, in 2 patients this was due to neoplastic infiltration around the cardia Once the cardia was passed, the view and rotating property of the gastroscope were undisturbed After biopsy the amount of bleeding was slight, frank hæmorrhage did not occur in any of the patients

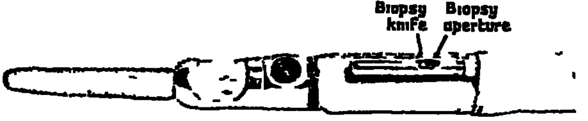

Fig 2—Distal end of instrument showing biopsy head in position of rest, and aperture partly open

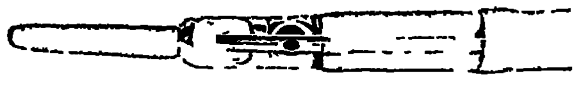

Fig 3—Biopsy head overlying viewing lens (black cross opposite biopsy aperture not shown)

The accuracy with which a specimen could be obtained by biopsy was found to be a matter of experience in handling the instrument This was also true regarding the number of failures at biopsy At only 53 of 60 attempted biopsies were specimens obtained In the second half of the series it was rare not to obtain a satisfactory biopsy specimen

During the trial it was found necessary to enlarge and modify the biopsy aperture because the amount of fragmentation of the earlier specimens was excessive, and it was doubtful whether a hard neoplastic mucosal lesion could be sucked into an aperture only 2 5 mm in diameter By changing the size and shape of the aperture as described the specimens taken were larger and less fragmented They contained full-thickness mucosa, muscularis mucosæ, and often a little submucosa (fig 4) Up to date we have obtained biopsy specimens of two carcinomatous lesions of the stomach, both radiologically negative but subsequently confirmed by operation In the later specimens all layers were well preserved, enabling detailed histological studies to be made This is important both from the diagnostic and from the research point of view

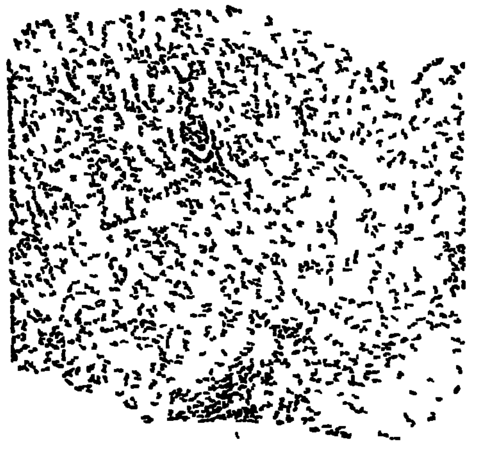

Fig 4—Biopsy specimen of normal gastric mucosa showing full-thickness mucosa, muscularis mucosæ, and some submucosa (Hæmatoxylin and eosin ×21)

Discussion

It is our view that the combined gastroscope-biopsy instrument offers great scope for more accurate diagnosis of gastric pathology With Benedict (1950), Shallenberger et al (1950), and Wirts et al (1951) we feel that the instrument can be used with safety in any patient in whom it is possible to perform gastroscopy, in our case using a modified Hermon Taylor gastroscope

At present it is too early to state that a biopsy specimen can always be obtained from an ulcer margin with accuracy, and that a neoplastic lesion can always be sucked into the biopsy aperture. Further, biopsy is confined to areas within reach of the gastroscope, which in many cases excludes the antrum Wirts et al (1951) found that with the Benedict type of operating gastroscope they were usually unable to obtain biopsy specimens from lesions high on the lesser curvature We have not encountered this difficulty

The same workers also mentioned the disadvantage of the reduced angle of vision in the objective of the operating gastroscope Both these objections have been overcome by using the Hermon Taylor type of gastroscope and Wood's gastric biopsy tube with its lateral aperture

Wirst et al found the increased diameter of the combined gastroscope more distressing to their patients, and rotation of the instrument into the anteroposterior position more difficult This has not been our experience

But with these workers we agree that it is difficult to keep the patient's stomach adequately inflated, because the air tends to escape through the cardia more easily

Incidentally Wirts et al mention that the use of Wood's gastric-biopsy-tube attachment would have possible advantage over the Benedict's forceps—a suggestion of which we were not aware when first experimenting with the instrument

Summary

A method of combined gastroscopy and biopsy under direct vision is described

60 patients have been biopsied up to date without any complications

We wish to thank Mr G Hawkins, of the Genito-Urinary Manufacturing Company, for his unfailing help in developing the biopsy gastroscope, Dr N F C Gowing, of the department of morbid anatomy, Royal Marsden Hospital, for much of the pathological work and for the photomicrograph, and our colleagues at both hospitals for referring their patients to us

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Preliminary Communications

PORTAL BACTERÆMIA IN ULCERATIVE COLITIS

JAUNDICE has, in our experience, occasionally complicated colonic excision for ulcerative colitis, developing within 48 hours after operation, full investigation failed to disclose hæmolysis as a result of blood-transfusions in any case This jaundice lasts for one or two days and invariably clears Its cause remained a mystery until the following case was seen recently

A man, aged 28, who had had an ileostomy instituted 8 years before, was submitted to panproctocolectomy 48 hours after this operation which was uneventful, his temperature rose with rigors to 106 5°F and he became jaundiced After 10 days his jaundice had subsided, though at the 5th postoperative day serum-bilirubin had reached 21 mg per 100 ml

The rigors and pyrexia in this case suggested the possibility of an infective cause for the jaundice Frank portal pyæmia seemed unlikely since jaundice had cleared spontaneously in all cases without antibiotic treatment, moreover, liver abscesses have not been found in any case of ulcerative colitis Portal bacteræmia was a possible explanation since the condition of the bowel would favour bacterial invasion of the colonic veins, thus leading to hepatitis without abscess formation since the hepatic reticulo-endothelial cells might be able to assimilate organisms though not septic emboli The following pilot investigation was therefore undertaken to ascertain whether bacteria invade the portal stream

METHOD

Controls had to be devised to eliminate the possibility that organisms may escape into the portal blood under normal circumstances and, further, when the intestines are handled at laparotomy Two samples of portal blood were therefore taken, one on opening the abdomen and the other at an advanced stage of the operation when the intestine had been manipulated Two control groups were chosen, one comprising patients with no lesion of the large bowel, and the second patients with a colonic lesion other than ulcerative colitis (table I)

Blood samples were obtained from veins draining the transverse colon in the first control group, and from veins near the lesions in the second control and the colitis groups It is easier to obtain blood by needle and syringe from a peripheral systemic vein than from a portal radical, for the vessel is less well supported in the mesentery and it is not possible to obstruct the venous return satisfactorily there while taking the sample We have found it most satisfactory to attach needle to syringe by a few inches of rubber tubing, one person then inserts the needle and holds it in place while another slowly withdraws the plunger

TABLE I—BACTERIOLOGICAL FINDINGS IN PORTAL BLOOD IN TWO CONTROL GROUPS

Group no	Case no	Sex	Diagnosis	Specimen no	
				1*	2†
1	1	M	Anastomotic ulcer	0	0
„	2	F	Gallstones, cholecystitis	Staph	Staph
„	3	M	Pyloric stenosis	0	0
„	4	M	Dissecting aneurysm	0	0
„	5	M	Carcinoma of pancreas, jaundice	0	0
„	6	M	Duodenal ulcer	0	0
2	7	M	Carcinoma of hepatic flexure	0	0
„	8	M	Carcinoma of sigmoid	0	0
„	9	F	Crohn's disease of sigmoid	0	0
„	10	M	Carcinoma of cæcum	0	0
„	11	M	Closure of colostomy	0	0
„	12	M	Hirschsprung's disease	0	0
„	13	F	Carcinoma of cæcum	0	0
„	14	M	Crohn s ileocæcitis	0	0
„	15	F	Carcinoma of cæcum	0	0

* Taken before handling gut † Taken after handling gut

Synchronous samples of systemic blood were not taken at the outset, but only after positive portal-blood cultures had been obtained for the first time and it was realised that these results might be open to attribution to generalised septicæmia unless bacteriological evidence to support the contrary clinical assessment was forthcoming

RESULTS

Tables I and II show the results

Controls (table I)

From only 1 of the control series, a case of cholecystitis, were organisms grown, these were non-pathogenic staphylococci

Ulcerative Colitis (table II)

Organisms were grown from 4 of the 9 cases of ulcerative colits—from 1 case (case 16) on two separate occasions, at primary colectomy and again six months later when the rectum was excised

DISCUSSION

In control case 2 (cholecystitis), where organisms were grown, these may have been contaminants, but this seems unlikely, since the blood samples could hardly have been taken under more aseptic conditions Moreover each blood sample was divided among five separate cultures, three from the first sample and two from the second being positive Chance contamination would hardly yield such profusion Schatten et al[1] reported portal pyæmia in 8 cases of a series of 25 with intra-abdominal lesions, none affecting the colon, staphylococci were cultured in

TABLE II—POSITIVE BACTERIOLOGICAL FINDINGS IN PORTAL BLOOD IN CASES OF ULCERATIVE COLITIS

Case no	Sex	Operation	Specimen no		Evidence of systemic infection	Comment
			1*	2†		
16	M	Colectomy	*Ps pyocyanea, Bact acidi-lactici Strep intermedius*	As in (1) plus *Cl welchii*	No blood culture No clinical evidence	—
		Rectal excision 6 mos later	*Staph albus*	*Staph albus* plus paracolon bacillus	Systemic blood at time of operation negative	—
17	F	Colectomy	*Esch coli*		No clinical signs of septicæmia before operation Blood-culture pos 3rd postoperative day, *Esch coli* grown but sensitivities different from portal-vein sample	1st sample from descending colon, 2nd sample from ileocæcal region, which was less seriously ulcerated
18	F	Panproctocolectomy		Paracolon bacillus, *Esch coli anaerogenes*	Systemic blood-culture at time of operation negative	—
19	M	Colectomy	Mixed staph	Pure *Staph albus*	Systemic blood culture at time of operation negative	Possibly contaminants

* Taken before handling gut † Taken after handling gut

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[1] Schatten, W E, Desprez, J D, Holden, W D *Arch Surg* 1955, 71, 404

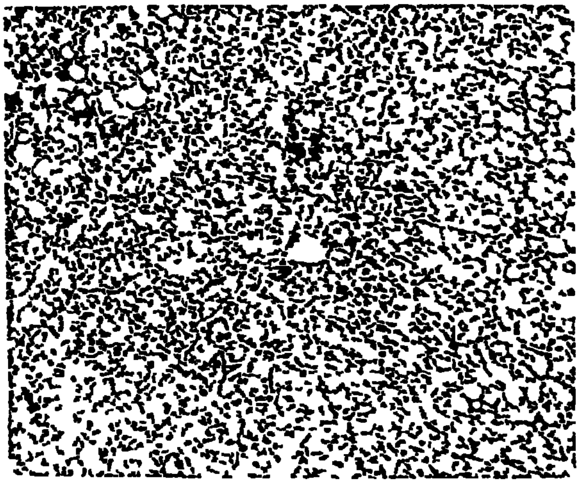

Fig 1—Case 2 section of liver showing peripheral lobular degeneration and fatty replacement

4 cases, all of cholecystitis That portal bacteræmia may arise spontaneously from time to time cannot therefore be ruled out

In 3 of the 4 present cases of ulcerative colitis where organisms were isolated from the portal blood, there can hardly be any question of this being due to contamination In the 4th case, where *Staphylococcus albus* was isolated, this is less certain Nevertheless this organism can be isolated from the bowel and may develop pathogenic qualities, in 1 case of ulcerative colitis previously reported,[2] generalised septicæmia due to *Staph albus* developed, and the patient died

The results in the first control group indicate that handling normal bowel does not produce a shower of organisms in the portal circulation, the same conclusion might be drawn from the second control group, but over half the patients in this group had carcinoma and in these cases every effort was therefore made not to handle the affected bowel In 1 case of the colitis group (case 17) organisms were discovered in the first sample but not the second, this may have been due to the fact that the second sample was taken from the right side, there the disease was less pronounced Operative manipulation seems to have increased the flora obtained at each of the 2 operations in case 16, and to have produced organisms for the first time in case 18

Could these results have been due to septicæmia or pyæmia? At 3 of the 5 operations (table II) systemic-blood samples taken synchronously with the first sample of portal vein blood were negative on culture, in neither of the 2 instances where systemic-blood samples were not taken did the patient show clinical signs of septicæmia at the time of operation, in 1 of these instances (case 17) the culture of systemic blood became positive for *Escherichia coli* three days after operation, but the sensitivities of this organism differed from those of the coliform organisms which had been grown from the first sample of portal blood Generalised septicæmia seems therefore to be an unlikely explanation of organisms isolated from the portal blood in these cases

Though jaundice did not develop in any of the 3, or possibly 4, cases of portal bacteræmia, severe liver damage was observed in the 2 cases where hepatic biopsy was undertaken, significantly, degeneration was pronounced at the periphery of the lobules—that is, in the vicinity of the afferent venules (fig 1) Fig 2 shows bowel wall with ulceration into the submucosal vascular plexus, the ulcer bed is highly vascular It is hardly surprising that it is in such cases, rather than those with relatively superficial ulceration in the mucosa, that organisms escape into the portal stream

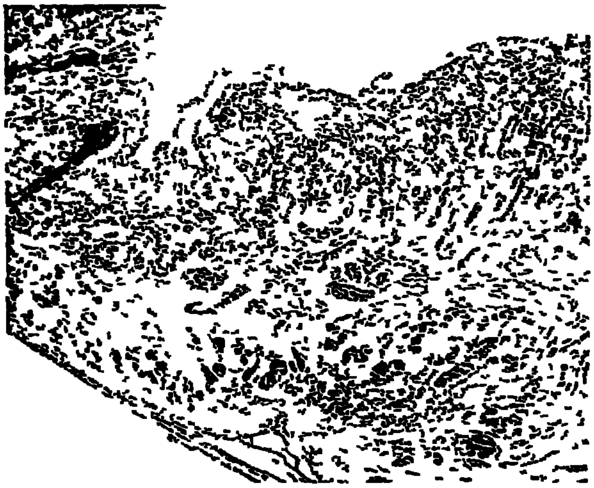

Fig 2—Case 1 ulceration has almost completely penetrated and destroyed muscle of colon wall, which is replaced by engorged vessels of granulation tissue

CONCLUSIONS

This pilot study indicates that portal bacteræmia may complicate certain colonic disorders, and in particular ulcerative colitis

We thank Dr M J Meynell and Dr H M Smallwood for their bacteriological investigations

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THE OCULAR COMPLICATIONS OF CHLOROQUINE THERAPY

Visual disturbances due to synthetic antimalarial drugs have been known since Reese[1] and Chamberlain and Boles[2] reported corneal œdema in American airmen who complained of blurred vision and haloes while taking prophylactic mepacrine in suppressive doses Their cases were exceptional among the large numbers to whom the drug was administered in this way, and these workers regarded them as a manifestation of idiosyncrasy, producing only a transient corneal disturbance which disappeared as soon as the drug was withheld

A more durable effect on vision was noted by Ida Mann[3] in workers engaged in the manufacture of mepacrine and in whom the severe blurring of vision was absent, but in her cases haloes were apparent from a deposit in the superficial layers of the cornea which was seen by slit-lamp microscopy to consist of fine yellowish dots This she believed to arise from direct contamination of the cornea by the mepacrine dust in the atmosphere of the works, and it and the symptoms were seen to subside in the affected persons when they were withdrawn from this work

In recent years the efficacy of such drugs, particularly chloroquine, in the treatment of some other diseases

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[2] Slaney, G , Brooke B N *Lancet*, 1958, i 504

[1] Reese F M *Bull Johns Hopkins Hosp* 1946, 78, 325
[2] Chamberlain, W P , Jr , Boles, D J *Arch Ophthal* 1946, 35, 120
[3] Mann, I *Brit J Ophthal* 1947, 31, 40

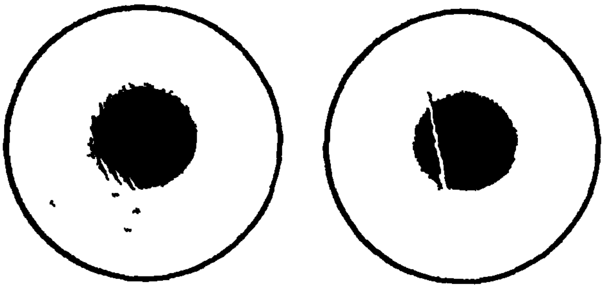

Fig 1—Lines of deposit in corneal epithelium (painting)

(notably lupus erythematosus and actinic dermatitis) has led to their empirical use in higher dosage, with which visual symptoms tend to develop more often Bleil[4] has reported from the United States the transient appearance of opacification of " the subepithelial layers and Bowman's zone " of the cornea, producing partial blindness as one of a group of severe symptoms in a patient under treatment with amodiaquine (' camoquin ') for lupus erythematosus, a finding which, from the description given, may be compared with the cases of corneal œdema reported by American workers in 1946 and referred to above

Here we draw attention to a more insidious and less transient condition resulting from the administration of chloroquine, it develops after an interval and on a dosage which shows considerable individual variation, it consists of visual disturbance associated with haloes suggesting congestive glaucoma and characteristic deposits in the corneal epithelium The details of the condition have been determined after the examination of 30 patients to whom chloroquine was being administered in various dosages and on different clinical indications 23 had lupus erythematosus, 4 actinic dermatitis, 1 chlorpromazine photosensitivity, 1 pityriasis lichenoides, and 1 infestation with *Clonorchis sinensis*, 28 of them were seen during or immediately after a course of treatment lasting from several weeks to two years To some degree these formed a selected group because, at the beginning of the investigation at least, they were those who complained of some disturbance

The 2 exceptions were both admitted for observation at the beginning of treatment so that early symptoms might be observed, we particularly wanted to know if epithelial œdema was an early change In both cases examination was negative, a finding which is perhaps of little value but may be correlated with the absence in the history of the other cases of any symptoms suggesting such a change in the early stages of treatment

Of the remaining 28 patients 19 complained of the following symptoms

	No of Cases
" Blurred " or " misty " vision	4
" Blurred vision and coloured rings round lights "	3
Focusing difficulties	3
' Sore eyes "	1
Various symptoms of drug intolerance*	8

* Described as photophobia, ' traffic dancing ', ' vision closing in ', " vision seemed not to register ', ' nausea and a drugged feeling ', &c

The spontaneous perception of haloes round lights was the presenting symptom in only 3 cases It was complained of by the patient who originally came to our attention and by only 2 others, and in all of them it occurred in special circumstances likely to demonstrate this diffraction effect—i e , while driving at night The appearance may be mimicked by causing the patient to view a naked light through a thin film of lycopodium powder, a test which is commonly used in ophthalmological practice to identify haloes of corneal origin, and when this was displayed to the patients under investigation 3 of them commented subsequently that they had become aware of seeing such haloes Although pathognomonic of such a corneal disturbance as is seen in these cases this symptom is clearly one which calls for a degree of perception which is not universal

Examination of these 28 patients by slit-lamp microscopy showed corneal changes in 22, but the apparent correspondence between this number and those complaining of symptoms is misleading because of the 9 cases who were asymptomatic 5 showed changes, severe in some of them, and among the 19 with symptoms no such changes were seen in 4 It is therefore evident that the complaint of some general visual disturbance is an unreliable guide

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[4] Bleil, D C *Arch Derm*, *Chicago*, 77, 106

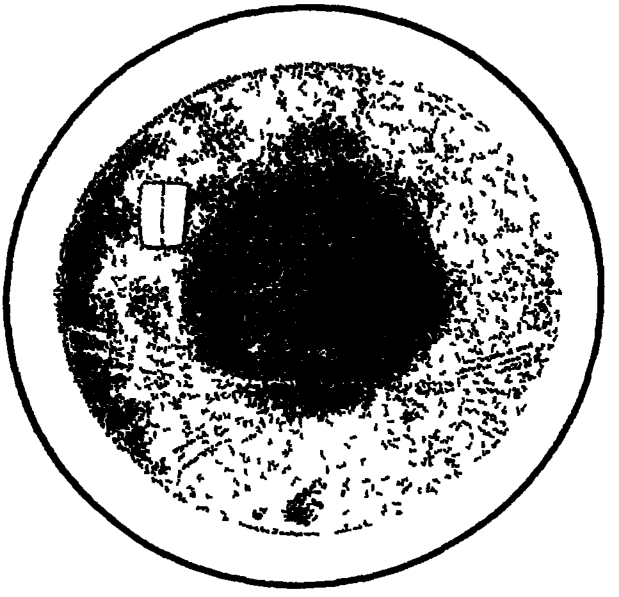

Fig 2—General epithelial deposit with incipient line formation (painting)

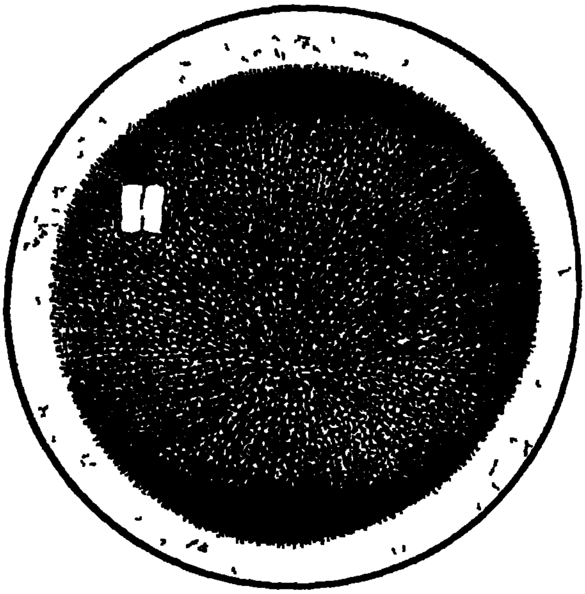

Fig 3—Severe general epithelial deposit (painting)

to the presence of the corneal changes which are characteristic in treatment with these drugs.

The changes seen were of several types, but all were confined to the epithelium of the cornea, with slight changes in the stroma immediately underlying Bowman's membrane in a few. In the first case which presented, the appearance (fig. 1) was that of an irregularly curved whitish line of deposit in the corneal epithelium, concentrated maximally just below the pupil and with white dots of deposit scattered irregularly over the corneal surface. 8 other cases showed this type of change, the line in some of them having taken on a yellowish pigmentation. In a further 6 cases the widespread white dots were present with a fainter, but more regular, aggregation into curved lines in the same position, an appearance resembling the lines of force of a magnetic field (fig. 2). In the remaining 7 cases the white dots alone were visible at the first examination. Fig. 3 illustrates the appearance in the patient infested by *Clonorchis sinensis*, in whom they were clearest. This appears to be the early stage of the keratopathy because it was seen to progress to the second type of change illustrated in 2 cases examined after a period of treatment, and in 1 further case this change was seen to progress to the complete picture with yellowish pigmentation of the subpupillary line. In addition there were 3 cases in which this fully developed change regressed after the cessation of treatment, in 2 of them with the complete absorption of deposits.

Apart from this picture, which we regard as typical of the condition, there have been other associated epithelial changes in the form of irregular limbal deposits (2 cases) and small maculæ (5 cases), sometimes in association with the typical picture and in other cases appearing separately, but in all of them in cases which at some time showed the typical change. Pigmented maculæ in the epithelium were seen in 2 patients who had ceased treatment and had originally presented a linear deposit.

The gradual evolution of these changes during chloroquine treatment and the more gradual recession seen in some cases when treatment has been discontinued make it fairly certain that they arise as the result of treatment with chloroquine. The time needed for their evolution and the relationship to the dosage used are still uncertain, partly because regular observation of all of these patients, drawn from a wide area, has been impossible, but also, we are sure, because individual reactions to the drug vary so widely.

The precise nature of these changes, therefore, their permanence, and their relation to dosage and duration of treatment, as well as the range of compounds by which they may be expected to be produced, are still uncertain and further investigations are being undertaken to elicit answers to these questions, but at least 1 case which we have under observation indicates that they may lead to continued loss of visual acuity, and for this reason we have thought it wise to point out the need for careful ocular supervision during treatment with these invaluable drugs.

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Reviews of Books

Rehabilitation after Illness and Accident

Editors T. M. LING, M.D., M.R.C.P., psychiatrist, Marlborough Day Hospital, London; C. J. S. O'MALLEY, C.B.E., M.B., medical director, Camden Road Rehabilitation Centre, and consultant in physical medicine, Queen Mary's Hospital, Roehampton. London: Baillière, Tindall, & Cox. 1958. Pp. 119. 12*s.* 6*d.*

"IT is probable," this book begins, "that in the history of mankind we can distinguish three stages in the attitude towards the disabled. The first . . . in which the disabled member of the tribe was left to his fate, or even liquidated. The second might be called the charitable stage. The third that of rehabilitation. Nowadays we are not satisfied with the maintenance of the disabled person, only with his rehabilitation as far as practicable to a full and normal life of work and leisure." This enlightened outlook is, however, still a new one. The best techniques for restoring the disabled are still being developed, and until Dr. Ling and the late Dr. O'Malley compiled this book no comprehensive text on rehabilitation had been written in this country.

In an easily read book, eight experts have in common a concise and forceful style—a welcome change in a subject on which many writings have been tediously hypothetical. They point straight to some of the important matters: "One out of twelve people in this country will be admitted to a mental hospital during their life-time. Nearly one half of our hospital beds are being used for the treatment of mental illness . . ."; "We have never known full functional recovery to be obtained if the patient is in danger of losing money thereby." And commenting on the need to teach doctors more about rehabilitation, "No question in this subject has ever been set in a qualifying examination for medical students." Finally, "Understanding and team work is not enough—another essential quality is the ability to handle human beings." Dr. O'Malley possessed just this quality; he died while the book was in the press, but the care and thought that he and his colleagues devoted to it make it a worthy memorial to him.

An International Nomenclature of Yaws Lesions

C. J. HACKETT, M.D., F.R.C.P., medical officer, venereal diseases and treponematosis section, World Health Organisation. Geneva: World Health Organisation. 1957. Pp. 104. 20*s.* Obtainable from H.M. Stationery Office, P.O. Box 569, London, S.E.1.

WIDESPREAD control of yaws on an international scale is impossible in the absence of a generally recognised classification of the lesions, and the nomenclature has grown up without direction and without a basis of systematic scientific observations. A great many terms are derived from picturesque folklore dating back to the slave days in the Caribbean, such as "yaws trash", "mother and daughter yaws", and "crab yaws". The difficulty of determining the order of appearance of the lesions is further complicated by latent periods and by relapsing lesions, which mean that some manifestations are wrongly attributed to particular stages of the disease. Now, thanks to Dr. Hackett, who has made a lifetime study of this many-sided disease, these defects have been remedied. He has provided a glossary defining all the acceptable terms in general use and discarding those which are misleading. A table sets out the appearance of the lesions in chronological order.

The great value of this work, however, undoubtedly lies in the 34 photographs, illustrating in a way never before achieved all the known manifold lesions. The illustrations are of a magnificently high standard, and they include 5 radiographs of periostitis and osteitis. The pictures alone make the book invaluable, and it should be in the hands of every doctor working in the tropics. A companion volume on syphilitic manifestations would be very useful.

Widows and their Families

PETER MARRIS. London: Routledge & Kegan Paul. 1958. Pp. 172. 18*s.*

THE third of the series of surveys by the Institute of Community Studies deals with the experiences of 72 widows who had lived in the East End of London, where the people are neighbourly and carry on a tradition of mutual help in trouble, and whose husbands had worked at the common trades of the area—in the docks and markets, the furniture, tailoring, and building trades, as drivers and mechanics On average, the widows had been married for sixteen years, and widowed about two when the survey was made a year or two ago, their average age was 41, and 61 of the 72 had children living The book deals first with emotional reactions to bereavement—apathy, a sense of futility and emptiness of life—and with certain associated changes 57 had difficulty in sleeping and 31 " some more or less lasting deterioration in health ", and 25 were left with feelings of hostility to society

Gone were the elaborate funerals of fifty years ago, with mutes in top hats and horses swathed in plumes, but the average cost of the funeral in this series was £57 37 of the husbands had been ill for upwards of one month before death, and 44 of the widows had been working before their husbands died 12 had remarried, and 82% of those who were still widows when the study was made were in employment 33 took a job within one month of their husband's death, the decision to start work being determined by their health, the ties of their children, the exhaustion of their savings, their loneliness, and, especially, by whether or not they had been working when their husbands died The average weekly income in widowhood was £7 1*s* 3*d*, about £3 less than that before widowhood All but 6 of the widows were receiving some kind of social-insurance benefit, mostly widowed mothers' allowance, and all but 3 of those without jobs had to claim National Assistance Few had anything in reserve

Mr Marris concludes that widowhood impoverishes social life, and that a fundamental limitation of National Insurance is its inability to protect the widow against loss of status, it could do so if it would provide benefits in addition to earnings, but it was framed in a harsher philosophy concerned only with the basic necessities of life

Understanding Your Patient

Editor SAMUEL LIEBMAN, M D, medical director, North Shore Hospital, Winnekta, Illinois Philadelphia J B Lippincott London Pitman Medical Publishing Co 1958 Pp 170 40*s*

THIS is a sketch by ten American psychiatrists of the common emotional problems and situations for which patients are brought, are sent, or come to doctors from infancy to grandparenthood The book appears partly in answer to the observation that 80% of " cases appearing for medical consultation " show " significant psychological factors in the genesis of their complaints " and partly to meet the complaint of many " professional men and leaders in American life " that many doctors fall short in recognising their patients' personalities and fail to attend to the whole man

Its multiple authorship is ironical evidence of the extreme fragmentation of medicine, of which, at bottom, these leaders complain, but the ten contributors cover their ground, and any reader who failed at the beginning to recognise his duty to his patient's personality will scarcely so fail at the end To the British reader the incursions of psychiatry into every province of medicine, hygiene, and, almost, human life may seem as striking as the intrusions of Psyche herself and perhaps a little disturbing, but it is instructive to read of the possible pattern of things to come

Chromatographic Techniques

Clinical and Biochemical Applications Editor IVOR SMITH, B SC, PH D, F R I C, lecturer in chemistry and biochemistry, Courtauld Institute, Middlesex Hospital, London London Heinemann Medical Books 1958 Pp 309 45*s*

FOR some years it has hardly been possible to open an issue of *Nature* and many another journal without reading of the application of paper chromatography or of column chromatography to the separation of yet another group of chemical compounds This book, written by a group of experts, deals with the applications of chromatography to clinical problems Nearly all of it is devoted to paper chromatography, but there are also sections on column chromatography (which uses as a supporting solid not paper but surface-active powders), particularly in its application to the separation and indentification of steroids There are valuable detailed descriptions of apparatus and techniques, many of them illustrated, and the discussion of the clinical interpretation of results is very helpful The chromatography of aminoacids and amines, indoles (including 5-hydroxyindolacetic acid), imidazoles, guanidines, purines, sugars, phenolic acids and acids of the citric-acid cycle, barbiturates, cholesterol, and steroids are all considered in detail The subject is growing very fast and no book about it could be up to date It would be easy, therefore, but not really constructive, to point out where additional information will have to be provided in the next edition

The editor and his nine collaborators have provided what is strictly a bench book, and there is little doubt that it will be a great success and find its way into almost every clinical laboratory

The Dermatologists' Handbook

ASHTON L WELSH, M S, M D, assistant professor of dermatology and syphilology, University of Cincinnati College of Medicine, Ohio Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1957 Pp 427 112*s* 6*d*

THE author's purpose was to bring together information on all the drugs about which the dermatologist should know He therefore describes not only those local and systemic agents used in the treatment of skin ailments but also a great variety of others which may give rise to drug eruptions There is in addition a great deal of irrelevant information more appropriate to a textbook of general therapeutics The material is factually accurate but it is difficult to see whom it will help, for nobody can learn from these pages how to select or administer appropriate treatment It is a useful source of information on American proprietary preparations

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Modern Trends in Pædiatrics (*2nd Series* London Butterworth *1958 Pp 385 70s*)—The high standard of the pædiatric volume in the first series, edited by the late Sir Leonard Parsons and published in 1951, has been maintained and in some respects enhanced in the new version, under the direction of Dr A Holzel and Dr J P M Tizard The 21 contributors, 15 of whom are British, 4 American, 1 Dutch, and 1 Russian, have covered all the main growing-points in pædiatrics—notably, experimental and human genetics, disorders in the perinatal period, mineral metabolism, corticosteroids in therapy, chromatography and electrophoresis, and the use of radioactive isotopes Contributions from a physiologist, a physicist, a biochemist, a pathologist, a virologist, a neurosurgeon, and a medical statistician, among others who are not pædiatricians, emphasise how progress largely depends on the concerted efforts of specialised workers The chapter on child psychiatry does not fully represent current opinion in this important and expanding branch of child health, constitutional and somatic factors are neglected, and the discussion of treatment is limited to psychoanalysis *The editors'* policy of asking each contributor to supplement an account of notable progress with a consideration of the outstanding problems and some speculation about possible future developments has infused a spirit of research into a valuable book which is a pleasure to read

Psychotherapy, a *Modern* Theory and Practice (London Staples Press 1957 Pp 334 30*s*)—A simplified approach to psychotherapy is here presented by a psychologist, Mr E Lakin Phillips, PH D It is based on the view that all behaviour results from the " assertions " that an individual makes about himself, as he chooses now one, now another line of action, other incompatible forms of behaviour are " interfered with " The aim of psychotherapy, therefore, is to make the subject aware of what he is asserting about himself Dr Phillips claims that this does away with the need for the Freudian concept of the Unconscious as the source of inexplicable behaviour Unfortunately his ideas are developed with much prolixity of style and that detracts from the value of the book.

THE LANCET
LONDON 7 JUNE 1958

Intestinal Angina

MANY manifestations of degenerative arterial disease are already amenable to operative treatment, but until lately surgeons have taken little interest in intestinal angina. This syndrome is in many respects analogous to angina pectoris and to intermittent claudication. Like these two conditions, it is a protest reaction of ischæmic muscle strained beyond endurance, but it is the smooth muscle of the bowel wall that is in revolt. The term "intestinal angina" may not satisfy the purist, but it is less grotesque than "intestinal claudication" and more descriptive than "abdominal angina".[1-5] There is every reason to believe that the symptoms arise from ischæmia of the intestine rather than of the abdominal viscera as a whole, and they must not be confused with the common abdominal radiation of cardiac anginal pain.

MIKKELSEN[6] described intestinal angina as "characterised by post-cibal generalised cramping abdominal pain that may extend to the back. The pain occurs a short time after meals and persists for one to three hours. Minimal at first, it increases in severity as the weeks or months pass. Association of meals with this pain soon leads to reluctance on the part of the patient to eat." MIKKELSEN's statement that the attacks strike "a short time after meals" must be interpreted liberally. There is often a silent interval of two to three hours, and the composition of the meal is as important as its bulk. The crucial relationship between meals and pain is easier to miss than the rapid and almost clockwork sequence of angina of effort or of intermittent limping. The patient who nibbles at his food during the day and takes substantial meals in the evening will suffer from nocturnal attacks, and when spontaneous remission of the pain follows alkali medication, the diagnosis of peptic ulcer will at once come to mind. Hospital regime, with its small, regular, and frequent meals, may put a welcome end to the attacks, or sharp paroxysms may give way to a dull, continuous ache. Vomiting appears to be rare even with severe pain, but persistent diarrhœa and a general decline in health may suggest some inflammatory condition or a malabsorption syndrome (the latter may, in fact, coexist). Finally, when loss of weight and loss of appetite are prominent, experienced clinicians will not easily abandon their search for malignant disease. Physical examination—though it may reveal generalised or localised abdominal tenderness, and during attacks even signs of peritoneal irritation—is not diagnostic, and, apart from the frequent but non-specific finding of occult blood in the stools, laboratory and radiological investigations are likely to be negative. Evidence of degenerative arterial disease in other parts of the body is too common to clinch the diagnosis, but it will strongly support it.

It is still difficult to assess the frequency of intestinal angina as a prodromal syndrome to acute mesenteric occlusion. It is certainly possible that mild attacks are often overshadowed in the minds of both patient and doctor by the ultimate catastrophe. Carefully reviewing the past histories of 12 patients with fatal mesenteric occlusion, DUNPHY and WHITFIELD[1] found that 7 had had attacks of "abdominal angina" for weeks, months, or years before their final illness, and in 2 of the 4 cases reported by BENJAMIN[7] and by MCCLENAHAN and FISHER[8] there had been warning episodes. MIKKELSEN[6] and MANDELL[4] mention other cases. On the other hand, several recent reviews of acute mesenteric occlusion and many standard texts do not mention prodromal attacks. It is of more than academic interest to decide whether this reflects their comparative rarity or lack of awareness on the observers' part: premonitory symptoms would offer today a nucleus of hope to patients whose prognosis remains exceedingly poor. In his review of 32 cases of acute mesenteric occlusion FORTY[9] found that none of the 19 patients who had been treated conservatively survived, that of a group of 7 who had been subjected to exploratory laparotomy only 1 survived, and that 4 out of 6 succumbed after bowel resection. It is true that many of these patients had one or several of the chronic ailments of old age, but this is a risk which the surgeons will have to contend with more and more. Commenting on this gloomy state of affairs (which has remained virtually unaffected by the use of anticoagulants and of broad-spectrum antibiotics), we suggested a few years ago that mesenteric embolectomy and thrombectomy were theoretically feasible,[10] and these operations have since been successfully performed.[11 12] It cannot be claimed, however, that such emergency surgery is within the scope of routine practice; indeed, even in expert hands it might carry a mortality even more forbidding than that of bowel resection. Prophylactic operations—practised already for threatened peripheral gangrene and for ischæmic heart-disease—may prove sounder, and plans for arterial grafting in one of MIKKELSEN's cases were abandoned only because of the erroneous interpretation of the aortogram.

Atherosclerosis of the larger and medium arteries primarily involves their bifurcations. At necropsy many aortas are almost completely free from atheroma, except where they give off their main branches, and at operation for acute mesenteric occlusion the distal vascular tree, though usually bloodless and collapsed, often shows no degenerative changes. At postmortem examination of 50 patients with widespread atherosclerosis CARUCCI [13] found involvement of the first two centimetres of the superior mesenteric artery in 33, but in none had the process spread distally Mesenteric arteriography, even when the roots of the vessels are scrutinised carefully, has many limitations The vascular network of the gastrointestinal tract is rich in anastomotic pathways, but their functional value under varying conditions is unpredictable Accidentally or deliberately, the hepatic artery has often been ligated, either proximally or distally to the gastroduodenal artery [14–16], and commonly the patient survives with no ill effects Accidental division of the superior mesenteric artery is one of the most dreadful calamities of the operating-theatre, but gradual obliteration is compatible with life [17, 18] Indeed, ROB and OWEN [19] *have recorded a case in which at operation* (for resection and grafting of a syphilitic abdominal aneurysm) all three branches of the cœliac axis and the superior mesenteric artery were found to be thrombosed they could be ligated and divided with impunity On the postoperative aortogram a greatly hypertrophied inferior mesenteric artery with a large ascending left colic branch appeared to be the only source of blood-supply to the abdominal viscera Generally, intestinal angina follows complete obliteration of the cœliac axis and narrowing of the superior mesenteric artery (or the reverse) [6, 20]

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[1] Dunphy, J. E., Whitfield, R. D. *Amer. J. Surg.* 1940, 47, 632.
[2] Berman, L. G., Russo, F. R. *New Engl. J. Med.* 1950, 242, 611.
[3] Sedlacek, R. A., Bean, W. B. *Ann. intern. Med.* 1957, 46, 148.
[4] Mandell, H. N. *New Engl. J. Med.* 1957, 257, 1035.
[5] Klein, E. *Surg. Gynec. Obstet.* 1921, 33, 385.
[6] Mikkelsen, W. P. *Amer. J. Surg.* 1957, 94, 262.
[7] Benjamin, D. *ibid.* 1948, 76, 338.
[8] McClenahan, J. E., Fisher, B. *Surgery*, 1948, 23, 778.
[9] Forty, F. *Brit. J. Surg.* 1957, 44, 458.
[10] *Lancet*, 1956, ii, 297.
[11] Shaw, R. S., Rutledge, R. H. *New Engl. J. Med.* 1957, 257, 595.
[12] *Lancet*, 1957, ii, 1328.

Apart from its importance as a premonitory syndrome, intestinal angina can be crippling enough to demand recognition and management in its own right A change in eating habits to light, small, and frequent meals is the obvious first line of treatment, but this will not be always effective Splanchnic nerve-block has been performed in at least one case with some success [21], and ganglion-blocking and vasodilator drugs have been tried What is needed most at present is better understanding of the natural history of the syndrome, and this can come only from wider awareness of its existence, its more frequent recognition, and its close observation

New Light on Molluscum Sebaceum

MOLLUSCUM SEBACEUM (molluscum pseudocarcinomatosum, keratoacanthoma) is a common pseudotumour, usually of the face, which grows rapidly in the space of ten to twelve weeks to form a firm nodule in the skin which, clinically and histologically, resembles very closely a squamous carcinoma, but, left alone, it shrivels within a few more months, discharges a keratinous plug, and heals leaving only a scar Its distinction from squamous carcinoma, with which it was long confused, is important but not very easy, depending on close cooperation between clinician and histologist Since we last discussed this lesion,[1, 2] many descriptions of it have appeared [3–6]

It has become clear that valuable analogies can be drawn from experimental cancer research This seems to have been realised first by HAMPERL and KALKOFF [7], but detailed ad-hoc experimental studies by WHITELEY [8] and by GHADIALLY [9] have proved the point, and have shown, moreover, that an obscure corner of experimental work may be itself illuminated by the human analogy It has long been known that, notably in rabbits, a substantial proportion of skin cancers produced by painting with carcinogenic materials regress spontaneously, especially if painting ceases, but it was generally supposed that these lesions were a frustrated form of squamous carcinoma WHITELEY and GHADIALLY have now both shown *that such regressing tumours* can be distinguished from the first from the non-regressing (" true ") tumours, being closely comparable to the human molluscum The non-regressing lesions begin as squamous papillomas or keratoses, arising from the surface epidermis, the regressing lesions, they both believe, arise from the hair follicles WHITELEY has shown in addition that in the rabbit the appearance of the tumours is related to the hair cycle After the whole flank has been plucked at once, active hair growth begins simultaneously over the whole area and continues for about thirty days, after which there is a period of quiescence that normally lasts for months When the flank is painted weekly with a carcinogen the cycle is speeded up, the inactive phase lasting only two or three weeks WHITELEY found that all tumours appearing during the phase of active growth are papillomas, while the regressing lesions of molluscum type appear only during the quiescent phase

Now it has been tolerably firmly established, by study of lesions in man,[3, 10] that the growth of the molluscum is not, as appears at first sight, an explosive invasion of the underlying tissues by epithelium growing downwards from the epidermis, but a proliferation of the epithelium of hair follicles and sebaceous glands The molluscum never grows deeper—a useful point in diagnosis—than hair follicles and sebaceous glands of the area In the nose and cheek, the sites of highest incidence, the hairs are small and downy and their roots superficial, while the sebaceous glands are larger and penetrate deeper, and it is the sebaceous glands chiefly that define the depth of penetration of the molluscum Not only does the hair-follicle complex lie deeply in the skin it is also, during part of its cycle of growth, naturally and normally invasive Sebaceous glands can disappear entirely, and their re-establishment, by growth outwards and downwards from the neck of the hair follicle, involves a kind of invasive growth into the dermis The inactive hair follicle is substantially shorter than the active, and re-establishment of activity involves a brief burst of downgrowth, or invasion, by the new hair germ[11] It is thus not at all difficult to understand that, while in most tissues invasiveness spells irreversible malignancy, abnormal proliferation of the hair-follicle complex may result in a burst of growth that is invasive yet not malignant

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[13] Carucci, J J *Amer J Surg* 1953, 80, 47
[14] Kehr, H *Münch med Wschr* 1903, 50, 1861
[15] Graham, R R, Cannell, D *Brit J Surg* 1933, 20, 256
[16] Rienhoff, W F, Jr *Bull Johns Hopk Hosp* 1951, 88, 368
[17] Moore, T *Brit J Surg* 1941, 28, 347
[18] Johnson, C C, Baggenstoss, A H *Proc Mayo Clin* 1949, 24, 649
[19] Rob, C G, Owen, K *Brit J Surg* 1956, 44, 247
[20] *New Engl J Med* 1949, 240, 262
[21] Boll, G *Zbl Chir* 1953, 78, 458

[1] *Lancet*, 1953, ii, 816
[2] *ibid* 1954 i, 89
[3] Calman, C D, Haber, H *J Path Bact* 1955, 69, 61
[4] Levy, E J, Cahn, M M, Schaffer, B, Beerman, H *J Amer med Ass* 1954, 155, 562
[5] McNulty, J R, Sommers, S C *Surg Gynec Obstet* 1957, 104 663
[6] Linell, F, Mansson, B *Acta radiol, Stockh* 1957, 48, 123
[7] *Hautarzt*, 1954, 5, 440
[8] Whiteley, H J *Brit J Cancer*, 1957, 11, 198
[9] Ghadially, F N *J Path Bact* 1958 75, 441
[10] Baumann, A, Lennox, B *Schweiz Z Path Bakt* 1954, 17, 326

Whiteley and **Ghadially** had already shown[12] that true tumours of the rabbit skin are commoner when painting is begun in areas of active hair growth; and this is not surprising, for in such areas the whole skin is hyperplastic and hyperactive It is equally believable that mollusca should arise at times of inactivity, for at this time the essential sensitive hair-germ lies near the surface, dormant awaiting the trigger action of the normal cyclic stimulus (unknown, but perhaps vascular[13]) to set it into sudden violent growth The carcinogen, it may be supposed, supplies the stimulus in the rabbit in an abnormal form, and so the growth produced is abnormal, but it is in the direction of normal new growth of follicles and lasts just about as long as the normal activity of the follicle In man most mollusca arise on the exposed skins of elderly people—in just the sites where, judged by the incidence of true tumours the effect of external carcinogens such as sunlight is maximal In younger men, and at other sites, there is a significantly frequent history of exposure to industrial carcinogens[14] It is thus not at all unreasonable to regard carcinogens as implicated in the lesion in man as well as in animals As **Whiteley** points out, the areas of maximal incidence are those where the inactive phase of the hair cycle is longest. Inescapably one must suppose that the molluscum is produced by the action of a mild carcinogenic stimulus on a group of resting hair follicles, exciting them to premature and perverted activity Perhaps because some minor mutation has been produced in the epithelium, perhaps because some external component of the complex machinery of the hair cycle is lacking, the growth is irregular and no differentiated products (hairs or sebum cells) result, but only non-specific keratin But the growth expands only to the anatomical limits of the normal full-grown follicle, and its growth ceases when the normal cycle would return to the resting phase. This seems, all told, a most reasonable explanation of a very remarkable lesion The idea that carcinogenic stimuli may excite intense but self-limiting bursts of proliferation in tissues normally subject to phasic activity is new, and may have other applications

An odd position, for which we must take some blame, has arisen over the nomenclature of these lesions In 1953 we suggested[1] that, since **MacCormac** and **Scarff**'s[15] original name of molluscum sebaceum was no longer tenable (being based on the hypothesis of origin from a sebaceous cyst, which was disproved) and **Rook** and **Whimster**'s[16] "keratoacanthoma" seemed unduly vague in anything except its unwarrantable assumption of neoplasia, the lesions might best be called "molluscum pseudocarcinomatosum" The name has found some favour, especially on the Continent,[6 7] but in effect this has meant that there are now three equal contenders for the title of one lesion We still dislike keratoacanthoma, but, since it has been shown so clearly that the lesion arises not (as we then supposed) from the epidermis but from the hair follicle and sebaceous glands, the objection to "molluscum sebaceum" is no longer valid This title has priority and should be accepted

A Fresh Start

No medical curriculum, however well devised, remains satisfactory for long, since undergraduate teaching should constantly take account of advances in knowledge and of society's changing needs Lately the preclinical course has been much criticised; and most plans for improvement have centred round reduction in its length and its integration with the clinical course Dr **Tanner**, in an address that appears at the beginning of this issue, recommends more radical reform Impressed by the doctor's "very wide field of operation" in "applied human biology", he calls for reconstitution of the preclinical curriculum to cover, in three years, "all the present ground of 1st M.B., 2nd M.B., and general pathology, but reorientated in consecutive courses entitled Cellular Biology. Organisation of Mammals, and Organisation of Man". These should prove understandable and attractive to the student who thinks of "medical practice as an endeavour to understand individual people in relation to their hereditary endowment, their upbringing, their family, their social position, and their whole culture, and as an endeavour to guide them, so far as may be, from childhood to old age through the squalls and doldrums so that they slip as seldom as possible over that invisible equator which divides health and disease, whether of mind or body" Certainly any student who receives such a preclinical education will not thereafter happily tolerate a clinical training consisting of "instruction by a multitude of specialists each on how to be an elementary specialist in his own particular field" (Even students who have had a more orthodox preclinical course can find their clinical years difficult and unsatisfactory "Training by a process of apprenticeship", writes a student, "works only when the master practises the trade that his students intend to follow"[17])

It should be possible, as **Tanner** says, now that the General Medical Council has given freedom and encouragement to experiment in medical schools, to put such a plan into action There would no doubt be some difficulty in introducing a preclinical course lasting three years, of which the first replaced the last year of study at school But the largest obstacle to fulfilling this plan—or any other well-constructed scheme of adaptation to current needs—is likelier to be that of finding a medical school with the courage, initiative, and determination to try it It seems probable that zeal less than **Tanner**'s, combined with the powers of reaction, will cause this scheme, like many another, to get no further than the curriculum committee, which doubtless will lay it aside after comfortably agreeing that it is nebulous and is not a "concrete plan", for only "concrete plans"—by which, we suspect, is meant detailed timetables—are heavy enough to replace the weight of tradition And timetables can be made only by a group of department heads and never by the single advocate of a new approach Hence it seems certain that no established school will undertake an experiment as radical as that advocated by TANNER But, if all the older schools are tied to their dead past, the same cannot be said of new schools, such as that of the University of Western Australia To break the mould of the existing curriculum it may be necessary to start in Britain a new medical school Its staff, drawn from many different traditions, might soon be fused into an enthusiastic team by competition with its orthodox rivals

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[11] Chase H B *Physiol Rev* 1954 34 113
[12] Whiteley H J Ghadially F N *Brit J Cancer* 1951, 5 353
[13] Montagna W Ellis R A *J nat Cancer Inst* 1957, 19 451
[14] [illegible] G W Johnson, H H *Arch Derm Chicago* 1955 71 66.
[15] MacCormac, H Scarff R W *Brit J Derm* 1936 48, 624
[16] Rook A J Whimster I W *Arch belges Derm* 1950 6, 137
[17] *Leeds Hosp Gaz* 1958 61, 42

Annotations

DIAGNOSTIC CENTRE FOR SOUTH LONDON

IN the years just after the war, the Pioneer Health Centre, established at Peckham by the late Dr Scott Williamson and Dr Innes Pearse, was one of the medical institutions in which our visitors from abroad showed most interest But by 1950 financial difficulties prevented its continuation on the original lines A decision was reached to dispose of the property to an authority prepared to use it for purposes related as closely as possible to the aims and objects of the founders, and in 1951 it was bought by the London County Council, under which it has continued as the Queens Road Health Centre The two departments of the Council with interests akin to those of the founders were those of public health and education The education department took over facilities including the swimming-pool and the gymnasium, and established a thriving institute for adult education which offered a wide range of classes—in dressmaking, millinery, pottery, and even boat-building The health department used the centre for a day nursery, for certain other maternity and child-welfare activities, and later for a child-guidance clinic For various reasons, it did not prove possible to start group practices for medical and dental practitioners, and the setting-up of a research unit consequently remained in abeyance, though the Minister of Health had expressed the hope that research would be undertaken, in which case he would consider assisting it The Sir Halley Stewart Trust, having been generous subscribers to the Pioneer Health Centre, retained their interest in the new Queens Road centre

In 1956 it became possible to make further progress General practitioners practising within a mile of the centre were invited to a meeting, with representatives of the Sir Halley Stewart Trust, the College of General Practitioners, the London Local Medical Committee, the South East Metropolitan Regional Hospital Board, and the local health authority, and afterwards 15 of them expressed their interest in the development of the centre At a subsequent meeting attended by 25 practitioners a subcommittee was formed to discuss details It was generally agreed that a close link with the College of General Practitioners was essential, and the Sir Halley Stewart Trust agreed to pay the expense of a medical director to organise and direct research at the centre over a period of five years, at a cost to them of over £12,500

Provisional plans have now been drawn up for adaptation of the building so that it will provide a diagnostic medical centre for the use of local doctors The cost of the internal adaptation will amount to about £16,000, of which the Nuffield Foundation is prepared to give £12,000 The grants from the Sir Halley Stewart Trust and the Nuffield Foundation are subject to the running costs being borne by the London County Council As a beginning, the intention is to offer, to all general practitioners in the neighbourhood, X-ray and pathological laboratory diagnostic facilities, and physiotherapy It is hoped that these doctors will be able to meet each other, more frequently, in the common-room of the centre, that they will have a closer link with consultants, who will discuss cases with them there, and that some of them will participate directly both in research projects affecting general practice and also in the training of medical students

PHYSICAL CHANGES IN THE PROLAPSED DISC

THE intervertebral disc in man comprises three distinct elements—the nucleus pulposus, the annulus fibrosus, and the cartilage end-plates of the vertebræ Eckert and Decker [1] stated that each of these elements degenerates with age The cartilage plate becomes thinner and its cellularity diminishes, and it may become torn In the annulus fibrosus swelling of the fibrous lamellæ and hyalinisation of the fibres may be seen, while the nucleus pulposus exhibits central fissuring, cavitation, and sometimes fibrosis and calcification These changes in the nucleus are associated with relative dehydration The normal nucleus consists of a three-dimensional lattice of collagen fibrils [2] in which lies a mucoprotein gel which is responsible for the hydrophilia of the nucleus With the increase in collagen and diminution of mucoprotein as a result of increasing age, hydrophilia is diminished

The mechanical behaviour of the nucleus pulposus when the spine is removed at necropsy has been analysed by Petter [3] and by Charnley [4] Its affinity for water may be a major factor in the production of back pain, indeed, its power to swell in the presence of water has been compared to that of laminaria Hirsch [5] noted that injection of saline solution into the intervertebral disc may produce severe pain in the back Changes in the fluid content of a disc may account for the attacks of lumbago which sometimes precede true prolapse of the disc

It is now generally conceded that trauma is not a large factor in the production of disc prolapse, and may often be absent The evidence for this has been summarised by Charnley, who contrasts the clinical picture of the disc lesion with that of spinal injuries Perhaps the common failure of the pain to subside with rest is the most cogent clinical evidence against the lesion being traumatic—apart, of course, from the absence in many cases of a history of injury or even of strain

Prolapsed discs removed at operation have recently been examined by Hendry,[6] who has determined their capacity to take up water, comparing this with that of the normal nucleus By comparing the weight of the removed nucleus after complete hydration in physiological saline solution with that after desiccation, it was possible to estimate the hydration of the prolapsed disc It is apparent that the deranged disc has a greater affinity for water than its normal fellow, but when the hydration is related to the dry weight of the disc it seems that the abnormal nucleus pulposus is in fact relatively hydrophobic in the body—that is, it is less hydrated when it is prolapsed than is the normal disc in situ.

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[1] Eckert, C, Decker, A *J Bone Jt Surg* 1947, 29, 447
[2] Sylven, B *Acta orthopæd scand* 1951, 20, 275
[3] Petter, C K *J Bone Jt Surg* 1933, 15, 365
[4] Charnley, J *Lancet*, 1952 i, 124
[5] Hirsch, C *Acta orthopæd scand* 1951, 20, 261
[6] Hendry, N G C *J Bone Jt Surg* 1958, 40B, 132

If changes in the disc precede prolapse these changes may consist, not, as is commonly supposed, in swelling of the nucleus but in relative dehydration, and the prolapse of the disc presumably results from undue compression strain on the annulus fibrosus. Relative desiccation of a degenerated disc would fit in with our knowledge of its structure, and with the changes which occur with age. On the other hand the gross degeneration in older people is rarely associated with prolapse. If desiccation in discs is a major factor in their prolapse, it is difficult to understand why the elderly remain relatively free from major disc derangements. In the patient with backache without sciatic pain, changes in the disc can still be a major cause of symptoms, and it seems more reasonable to assume that the sudden episodes of back pain are due to an increase rather than a decrease in tension within the disc. It is quite clear that further studies of the physical properties of the intervertebral disc are essential.

EMERGENCY RESUSCITATION

IN the emergency resuscitation of someone who, for whatever reason, has ceased to breathe, the most important and urgent necessity is to introduce oxygen into the lungs, preferably in a volume sufficient to allow carbon dioxide to be removed. For this it is important that the airway is kept clear, which entails not only removal of any foreign material that may be there when the patient is first seen, but also the prevention of further foreign material, particularly vomitus, from entering subsequently. In practice this almost inevitably means treating the patient in the prone, not the supine, position. A subsidiary but important point is that the minimum strain should be thrown on the circulation, whose integrity is impaired in many of the conditions in which emergency resuscitation is needed.

If mechanical apparatus is to be used successfully for this purpose it must be easy to use and reliable, and the manufacturers must make it quite plain what serviceing is needed and at what intervals. It is unrealistic to expect people unused to this type of apparatus to service it efficiently without special instructions, and the manufacturer must emphasise this if he wishes his apparatus to be used with success. The lay press has recently extolled a resuscitation machine for use by trained lay people, notably ambulance men. This machine is intended to assist patients who are apnœic by providing artificial respiration by intermittent positive pressure. Two questions arise in connection with such a device. First, in what circumstances is it likely to be needed? Second, is it technically satisfactory?

In many large industrial concerns a workman may need artificial respiration, either because of poisoning by carbon monoxide or an industrial solvent such as trichloroethylene, or because of electric shock. The situation is ideal for rapid and efficient treatment, for the victim is likely to be discovered quickly, and large industrial concerns run their own well-trained emergency service, often headed by a doctor, which can be on the spot within a very few minutes. In such circumstances a resuscitation machine may prove a useful item. In domestic practice, however, the situation may be very different. Victims of coal-gas or barbiturate poisoning are often not discovered for a long time, and the point of primary importance is to get an ambulance to the victim at the earliest possible moment after the alarm is given. This is much easier now that many ambulances are in radio communication with their headquarters. It is not practicable to carry a resuscitation machine on every ambulance, and it would be a retrograde step if any delay was introduced by instructions that such a machine must be fetched. The Holger-Nielsen method of manual artificial respiration is easy to learn[1] and effectively ventilates the lungs.[2] It is questionable whether it is not better to use this method of artificial respiration (or one of its modifications) and transfer the patient to hospital than to rely instead on apparatus which may not be immediately available, which may be imperfectly familiar to the operator, and which may from disuse be out of order.

The apparatus described runs off an oxygen cylinder, which is also used to operate a sucker. It is excellent that a sucker is provided and that the accompanying instructions emphasise the importance of a clear airway, but the value of this is lost because the patient is normally treated supine. Even a skilled anæsthetist cannot protect a patient from the danger of inhaled vomitus in this position. At the end of expiration subatmospheric pressure is applied to the trachea—a feature which is rightly claimed to assist the venous return to the heart.[3 4] The benefit of this, however, is entirely dissipated because expiration is slow—far slower than would be acceptable in any machine for long-term positive-pressure respiration—so that the mean mask pressure, a principal factor in determining the effect on the circulation,[3 4] is unduly high. Emergency resuscitation by intermitted pressure respiration should be further tested. But if apparatus is to be used it should be reliable, and hence simple.

FERTILITY

PAPERS read at the annual conference of the Society for the Study of Fertility, held in London on May 29–31, testify to the intricate constitution of human fertility. Small wonder that infertility is attributable to a host of different causes, and that inquiry into the attendant problems involves widely differing disciplines. Clinical investigation plays an essential part, not only in the development of palliative and sometimes of remedial measures, but also in permitting, under favourable circumstances, definition of specific problems for the guidance of basic research.

Clinical study is perhaps most rewarding when morphological abnormality is found to be the essential cause. The patulous cervix, for example, can be implicated in many cases of spontaneous abortion, and the simple operation designed to reinforce the cervical musculature, was described by Mr V B Green-Armytage, it is reported to maintain pregnancy in most cases. On the other hand, recourse to some operative measures may not be justified even though a priori they seem rational. Mr H H Fouracre Barns described a careful analysis of numerous cases of uterine retrodisplacement which showed that the condition should not be held responsible for infertility. Pathological states less obviously connected with the reproductive process may be potent sources of failure. This was well brought out by Mr Linton Snaith and Dr G R Peberdy (Newcastle upon Tyne), who maintained that emotional stress may induce demonstrable abnormalities of function in the female genital tract.

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Dr Bernard Sandler (Manchester) adduced strong evidence that comparatively minor infections of the nasopharynx can be causally connected with infertility, eradication of the invading organisms, which may or may not simultaneously infect the cervix uteri, was in most instances shortly followed by normal pregnancy By contrast, even though endocrine function is fundamental to reproductive function, endocrine therapy in cases evidently involving hormonal imbalance is notoriously disappointing Dr Margaret Jackson (Crediton, Devon) reported that administration of some of the new oral progestogens was consistently of small value for the maintenance of pregnancy, though they were often effective in the treatment of leucorrhœa and amenorrhœa

In the research field, Miss H M Bruce reported a more encouraging finding—namely, that a course of treatment with the progestogen 19-norethisterone induced ovulation in mice, apparently by a kind of release mechanism, immediately after treatment was stopped Observations indicated that, during treatment, ovulation and vaginal œstrus were suppressed, psychic œstrus was displayed at intervals, but coitus was *not followed* by pregnancy Possible causes of infertility in man were suggested by other papers based on research projects Arguing on analogy between mouse and man, Dr A J Bateman (Manchester) pointed out that embryonic death in the first week, or associated with miscarriage at 28 days and $2^1/_2$ months after conception, may reasonably be ascribed to the development of dominant lethal mutations—a hypothesis that is especially important in view of the increasing radioactivity in the world today and its acknowledged mutagenic effect

These and other communications at the conference support the idea of fertility as a state directly maintained by many and varied endogenous and exogenous influences, and dependent on the functional and structural integrity of the germ-cells, which in their turn are at the mercy of many different agents It is perhaps one of the most diversified of biological phenomena, offering rich opportunity for intellectual adventure and experimental investigation

THE WAALER-ROSE FACTOR IN RHEUMATOID ARTHRITIS

THE discovery by Waaler in 1940[1] and independently by Rose et al in 1948[2] that the serum of patients with rheumatoid arthritis could potentiate the agglutination of sheep cells sensitised with rabbit amboceptor imparted a tremendous impetus to serological research into the "collagen" diseases As a result of the work of the past ten years it is now definitely established that the factor responsible is found almost exclusively in rheumatoid arthritis

Many attempts have been made to isolate the factor in a pure state, and it is generally agreed that, although some of the earlier studies suggested that it belonged to the β-globulins, electrophoretically it behaves as a -globulin Apparently the earlier confusion was due to a tendency for the factor to migrate with the β-globulins when these are present in their absence the factor undoubtedly moves with the γ-fraction A simple method of effecting moderate purification was introduced by Svartz and Schlossman in 1953[3] They found that dilution of the serum with distilled water followed by cooling to 4°C led to a precipitate in which most of the activity was retained When redissolved and electrophoresed on a starch column this cold-precipitated material moved as a single band with a speed corresponding to a fast -globulin Since the active factor could not be further purified by this technique, Svartz and her colleagues[4] turned to ultracentrifugation A top and a bottom fraction were thus obtained with an obvious concentration of the active factor in the bottom fraction, but repeated centrifugation led to loss of activity Final purification was achieved by ion-exchange chromatography on carboxy methyl cellulose—a method by which Lospalluto and Ziff[5] had already achieved a 500 fold concentration The product obtained by Svartz *et al* when they subjected the cold-precipitated fraction to this type of chromatography is apparently a single substance judged by chromatography, electrophoresis, and ultracentrifugation Its sedimentation constant is 18 7S

These results of Svartz et al do not agree completely with those of Franklin et al[6] at the Rockefeller Institute, New York They find that on ultracentrifugation of whole serum the rheumatoid factor is almost entirely concentrated in a fraction whose sedimentation constant is 22S This heavy fraction is readily dissociated by 6*M* urea into two fractions of 19S and 7S, the 19S fraction retaining the biological activity of the rheumatoid factor It seems probable, therefore, that differences of technique between the two groups of workers favour association in one case and dissociation in the other From the closer correlation between biological activity and concentration claimed by Svartz et al it seems that their fraction with sedimentation constant of 18 7S must be regarded as the purer

When the differential agglutination test was first described most investigators believed that the serum factor promoted agglutination reactions in much the same way as albumin and other macromolecular substances promote agglutination But more recent work has shown that the rheumatoid factor reacts in a more specific fashion with γ-globulins from a wide range of species The reaction does not involve normal γ-globulin in its native state but γ-globulins that have undergone denaturation as a result of ageing, heat, or specific interaction with antigen Glynn, Holborow, and Johnson have therefore suggested that the Waaler-Rose factor is probably an antibody to γ-globulin, not in its native state but to reactive groups exposed as a result of denaturation and shared by the globulins of many different species The mechanism is similar to that described by Coombs and Coombs[8] as producing immunoconglutinin—i e, the exposure of antigenic groups on complement as a result of an unfolding of the molecule when it is absorbed on an antigen-antibody complex The ultracentrifugal demonstration of the existence of the rheumatoid factor as a readily dissociable complex with other components of the γ-globulin complex may be a manifestation of its antibody nature with a specificity for reactive groups in other γ-globulins We agree with Franklin et al[6] that "the possibility that the 22*S* component might represent a soluble antigen-antibody complex appears worthy of investigation"

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Special Articles

SOME PROBLEMS OF PSYCHIATRY IN PATIENTS FROM ALIEN CULTURES*

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A RECURRENT theme in anthropological studies of primitive societies has been the myth of psychosis-free cultures.

Ellsworth Faris (1937) thought schizophrenia non-existent among the forest Bantu, and Seligman (1929) thought it unknown in New Guinea, Lopez (1932) thought none was to be found in the Brazilian interior. Laubscher (1937), however, found no lack of mental illness among the Cape Bantu, and considered schizophrenia their commonest form of psychosis. In 1945 Maloney revived the myth in favour of the Okinawans, but in 1952 Wedge showed that rates for psychotic breakdown were higher in Okinawans than in any of the other immigrant groups in Hawaii. In Formosa, Lin (1953) found prevalence-rates of the major psychoses which are not unlike those shown by European populations.

Mention should also be made of exaggerations in the opposite direction. One American anthropologist, of great distinction as an anthropologist but perhaps less well versed in abnormal psychology, studied the inhabitants of the Melanesian island of Alor for a year and a half and came to the conclusion (which was only strengthened by an analysis of their Rorschach responses) that they were all fundamentally schizophrenic (Du Bois 1944). Yet somehow they survived, and fended for themselves, and married and reared families.

Although in fact there seems to be no social group which is *immune* from psychotic breakdown, the relative incidence of the major forms of psychosis may be quite different in different societies.

Kraepelin, in 1909, was struck in Java by the paucity of cases of well-marked depression "such as fill the observation wards at home", Carothers (1953) and Laubscher (1937) have both remarked on the rarity of psychotic depression among Africans—in Kenya and in South Africa respectively. In a "true prevalence" study, not dependent (as were the other observations) on hospital admission figures, Lin (1953) showed that the ratio of schizophrenic to manic-depressive cases, which is about 3/1 in European surveys of this kind falls to 2.5/1 in his Formosan population. (On the other hand, alcoholism and psychopathy were almost unknown in Formosa.)

My own experience in India was on similar lines. When I lived for a year (and practised medicine) in a village of 2400 inhabitants, I was aware of only one case of severe depression—and that did not last long. In his practice in Leicestershire Watts (1956) would expect to see 12 cases of psychotic depression in a group of this size during the course of a year.

Not all the evidence points in this direction, however. A study of the Hutterite community in North America (a farming community, of the Anabaptist sect, who practise a primitive Christian morality, holding all worldly goods in common, and who are remarkable for their strong sentiment of brotherhood and solidarity) showed that this community was *not* immune from mental illness, as some visitors had reported but among them depressive psychosis was much more frequent than schizophrenia (Eaton and Weil 1955).

Another legend which dies hard is the assertion that there are forms of insanity peculiar to the members of particular cultures. There is *some* truth behind this assertion, for conditions such as *witigo* among the Ojibwa and Cree tribes in Arctic North America, the celebrated running *amok* of the Malay, or the *utukwasa* of the Cape Bantu have a content which is imposed by their particular cultural tradition. Yet the form of the illness is found to correspond to a familiar, indeed a universal, pattern. Knowledge of the relevant cultural stresses may be important in the anticipation of acute illnesses of this kind, and in the aftercare of any patients who may recover from the acute psychotic breakdown, but it is less essential for the diagnosis of the established condition. (An exception to this generalisation is that in West Africans organic psychosis, especially that due to trypanosomiasis, can easily be mistaken for schizophrenia (Tooth 1950).) The gait, the posture, the expressive movements of a catatonic, a manic, or a melancholic patient have a remarkable similarity, whether he be a Japanese, an Indian, a Dutchman, or a Scot.

There is, however, no such reassuring familiarity when one approaches the diagnosis of psychoneurotic or psychopathic states.

Culture and Neurosis

Unfortunately, tolerance and respect for the values and customs of alien cultures do not seem to be natural attributes of mankind. They have to be learnt, and many people have strongly resisted this type of learning. Formerly, the observation and analysis of alien cultures was of interest primarily to anthropologists, but in recent years psychologists also have found that the study of man in society is an essential part of their discipline. It has come to be generally accepted that social learning enters largely into the formation of normal and abnormal personality.

Indeed, studies of personality in culture (see Hallowell 1952, Mead 1952) have altered the whole concept of psychological normality. Not merely have they greatly extended our appreciation of the possible range of normal human behaviour, but rather a new dimension has been recognised—the cultural dimension.

This is most apparent (Benedict 1934) in compact homogeneous societies, which offer a very restricted choice of forms of approved behaviour to their adult members. Each of these societies has a very clear picture of what it considers normal or well adjusted, and the range of socially approved personalities in various cultures is wide indeed.

For example, the Comanche were one of those very warlike American Indian tribes whose boys were schooled from infancy in stoicism, courage, ferocity in combat, and boastful self-assertion. The Comanche shared with other tribes, such as the Navaho, a vigorous belief in the immanence of spirit forces. In these Plains tribes it was a necessary and expected event in the life of every young man that he should have certain hallucinatory experiences, in which the spirits would appear before him and give him significant advice. In these communities a man might be seriously handicapped in life because, in spite of undergoing strenuous ordeals, he did not succeed in experiencing this vision.

In complete contrast are the Zuñi Indians. Their culture sets such store upon passivity, conformity, and individual self-effacement that a person who is so "abnormal" as to display undisguised personal initiative, ambition, and drive runs a grave risk of being branded as a wizard and hung up by his thumbs (Mead 1939).

It seems, in fact, that each society lays particular emphasis on one or other of the many possible patterns of human behaviour. Those individuals who show this type of personality in high degree will be its leaders and its saints, those who develop the dominant traits to a slighter extent will be its rank and file, and those who, for innate constitutional reasons or because of some peculiarity in their upbringing, express a bias towards an alternative pattern of behaviour may find themselves regarded as delinquent or insane To the average man the demands of his society seem right and natural, but to the deviant they may seem nonsensical, unreal, and wrong

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* Based on a paper read before the Section of Psychiatry of the Royal Society of Medicine on Feb. 11, 1958.

It is worth remembering, too, that similar differences may be apparent in the same society at different times Persons who were regarded as saintly in medieval England might well be diagnosed as schizophrenics today, and, on the recommendations of the recent Royal Commission, some famous Elizabethans might be detained as psychopaths

If, then, cultural influences so largely determine the concept of normal human behaviour, it is essential that the parameters of the normal should be clearly known before we diagnose a person as abnormal But in fact they are not always known A British psychiatrist practising in East Africa wrote ten years ago "We in Africa have not got a Normal for our basis, because we have never taken the trouble to study African Normality We have so far judged our cases on their departure from a European Normal, if we have judged them at all" (Mackay 1948) Since then Carothers (1953) has made a spirited attempt to make good the deficiency, but African critics of his monograph on the African mind have not hesitated to point out that he still tends to depict it as an imperfect version of European mentality rather than as a separate personality pattern—or group of patterns, because African culture is much too diverse to be included in one descriptive category

Europeans have been slow to make the effort to learn the dimensions of normal behaviour in alien societies, but this is no longer the concern only of Europeans In increasing numbers our African, Indian, and other Eastern colleagues are also specialising in psychiatry, and already they have begun to show an awareness of the cultural dimension in psychiatric diagnosis, and an awareness, also, of the fact that a medical curriculum modelled strictly on Western lines may not adequately prepare them for practice in their own countries

Advantages of Sorcery

When practising medicine in villages of northern India I became familiar with some of the pitfalls which beset the diagnosis and treatment of neurotic disorders in an unfamiliar culture Needless to say, misunderstandings commonly arose between my patients and myself At first I was rather surprised that so many of my village patients offered me their wrist, without my asking, as if expecting me to feel their pulse It was only after several months had passed that a man highly regarded in that district for his possession of magical charms, explained to me that my patients were not concerned about their pulse, they believed that I, like other local healers, could tell by the quivering of the tendons in their wrist what kind of witch, demon, or sorcerer was responsible for their illness

It was from the village *topi-wala*, or cap-maker, that I learned an essential part of medical practice in this community when you treat a patient, no matter how grave the prognosis or how uncertain your remedy, the treatment must always be accompanied by the formula "Do this, and take this, and you will *certainly* recover" To fail to give this assurance was regarded as malpractice—it was tantamount to saying "I don't care if you get better or not" In a community where magic, sorcery, and potent incantations were firmly believed in, such an attitude could readily be interpreted as a hostile attack

In this countryside major infections are common dysentery, typhoid, smallpox, pneumonia, and tuberculosis all took their toll, and each serious illness tended to be aggravated by fear of the malevolent supernatural agency threatening the patient's life I came to recognise that the local healers whom the villagers were accustomed to consult did them a real service in allaying this acute anxiety, even though they might do little to influence the course of the infection This was brought home to me by a rather humbling experience

One night a bullock-cart drew up on the roadside near the village where I was living, and I was asked to see a patient He was a thin middle-aged shopkeeper from a village some fifteen miles off and appeared to be very ill So far as I could judge, he had recently had typhoid fever, and during his convalescence he had developed severe heart-failure He was breathless and very frightened, his liver was enlarged, and his pulse-rate was over 130

I gave him a heroic dose of digitalis, and next day, finding him no better, repeated the dose Next morning I found him a changed man, quieter, less dyspnœic, and with a steadier pulse, but I could not take the credit for his recovery He explained to me now that he had indeed been on the brink of death because an enemy had put a deadly charm on him, but just in time he had found a healer with a still more potent counter-charm This healer had branded the back of his neck with a red-hot iron and exorcised the evil influence

I saw this patient in his home once or twice more during the next few weeks He developed cardiac œdema and died, but he died tranquilly

This case was a reminder that acute anxiety cannot be relieved by reassurance unless, first, it has been fully abreacted and this patient had been unable to tell me about his *real* fear, when he most needed help, because, being a white sahib, I quite obviously could not understand about such things

At the time I was a little hurt, even a little angry with this patient for his perversity in rejecting the "realistic" help which I offered him and for being so obviously benefited by the magical help which he received from my rival practitioner, but the experience was repeated so often that I soon became accustomed to it

Dissociation and Surrender

Probably the most frequent expression of what *we* should call a psychiatric disorder, among those Rajasthani villagers, is the phenomenon of hysterical dissociation The capacity to pass into a trance-like state in which normal consciousness is suspended while an alien spirit takes over and speaks through one's lips is highly developed in this community, everyone sees it happen to others and expects without question that in similar circumstances it will happen to oneself—and it does This institutionalisation of trance-like states is, of course, something which is found in many parts of the world, and not only in primitive societies On my return from India I read for the first time the paper by Sargant (1949) describing the states of dissociation which he saw being induced during highly emotional revivalist meetings of the snake-handling religious sects in the southern States of America, and I was reminded at once of the rhythmical hymn-singing and the mounting fervour which led to a similar climax in our *satsangs* in north India Both of these, it might be pointed out, are socially approved extensions of the limits of normal experience rather than signs of abnormality, but in India, I found, states of dissociation occurred in many other contexts as well.

I have already mentioned that most physical illnesses were aggravated by a fear of supernatural powers at work. Often, either spontaneously or with prompting from a man who knew healing charms, the patient would surrender his consciousness to the responsible witch or evil spirit. Two things impressed me in thinking over the many incidents of this kind which I had seen. First, how readily it came about. In our more educated and more sophisticated communities we deplore such excessive surrender of self-control, but perhaps we lean too far in the other direction: certainly Shorvon and Sargant (1947) have shown that, at times, a total surrender of our customary restraint and self-consciousness in a violent emotional abreaction can relieve us of a burden of pent-up anxieties. Secondly, I was impressed by the explicit way in which the terrifying fantasies accompanying sickness found expression in these trance states, and so could be dealt with—but not by me, so long as I remained a sahib, someone from the outside world who did not understand about the witches, ghosts, and demons whose presence was felt to be so close and so threatening.

Barriers to Communication

One does not, of course, have to go so far afield to find instances of this type of barrier to communication: it occurs commonly in the general practitioner's surgery, and one of its commonest forms, as Donaldson (1958) reminds us, consists in the patient's reluctance to reveal the cause of his anxiety—about cancer, for example—for fear of being laughed at. Another general practitioner, who has demonstrated his ability to deal with minor mental disorders in his surgery, has emphasised that the most important thing is to be able to sense when a patient is trying to tell you what is really the matter, and to help him to put it into words (Model 1957).

To do this successfully, two attributes are necessary in the doctor—a thorough familiarity with the patient's personal background (such as the general practitioner commands par excellence) and the ability to convey to the patient that whatever he says will be listened to sympathetically and without ridicule.

In the case of African and Oriental patients who consult us in this country, particularly in students from overseas, we seldom know as much as we should like to do about the cultural background to their personal problems, and so it becomes doubly important that we should succeed in winning their confidence. In these interviews we do well to remember that many of these young people are, perhaps for the first time in their lives, being compelled to fend for themselves without the support of their kinsfolk—and this in an environment which is profoundly unfamiliar in all the unconsidered details of daily living. In these circumstances, a certain hypersensitiveness or even a paranoid outlook must be considered a natural rather than an abnormal reaction.

Sometimes, once confidence has been established, the presenting problems of these overseas students can be dealt with on a fairly superficial level. But often it is not so simple, especially when the most important factors in the mental conflict are not readily accessible in the patient's consciousness.

The example which comes to my mind is the syndrome known to my patients as *jiryan*, or "loss of semen." I have described elsewhere (Carstairs 1956) the clinical features of this syndrome. In brief, it consists of a chronic anxiety state in males, in which the patients complain of exhaustion, inertia, and wasting away of the bodily tissues, although they appear normally robust on inspection and are capable of vigorous exertion in emergencies. It is, in fact, akin to effort syndrome, but instead of ascribing their weakness to heart-disease these patients are convinced that it is due to the leaking away of their semen, in which (they believe) reside the health and strength of the body. Nor is this merely a conscious rational fear—as cancerphobia often is. It is very deepseated and persists in spite of the assurances of quacks and medicine-men of all kinds.

I believe that *jiryan* is the commonest form of anxiety neurosis among men of the few Indian communities which I know well, and I ascribe it to certain characteristics of their upbringing, particularly the relationship with the father, which is so patterned as to emphasise œdipal tensions yet also to make it difficult ever wholly to resolve the œdipal complex. The upbringing of a high-caste Hindu boy in these communities requires that he accept a multitude of restrictions in which the two dominating themes are deference to his father and to all father-figures, and severe restraint in his emotional life—especially in the presence of his elders. A married son continues, as a rule, to remain in his father's household, but etiquette demands that he should deny himself any expression of independence, and even act as though he did not experience a sex life of his own. In these joint families, a son must ignore his wife if his father or his mother is in the room, if he wants to say something to her, he has to address his remarks through his elders.

It is against this background that we have to evaluate the constantly recurring complaint of loss of semen, with its attendant feelings of weakness and impotence. Here neither magical reassurance nor the quack remedies which are to be found advertised in profusion in the Indian press can give lasting benefit. The patient needs to be helped to recognise his real fear, which is the fear of offending his all-powerful father, before he can begin to master this recurrent anxiety which haunts his progress towards emotional maturity.

In this, as in the other instances which I have cited, the emotional ingredients of the syndrome are familiar enough, but they find expression in particular patterns of behaviour which at first we may have difficulty in recognising and in interpreting correctly. There is, I am sure, no short cut to the very full and sensitive appreciation of the nuances of a culture which is necessary if one is going to attempt deep psychotherapy. Many distinguished psychoanalysts have shown themselves capable of insight into one or more cultures besides that in which they were reared, but the more profound the psychological exploration the further it must go into the recesses of the patient's cultural origins. Writing from Buenos Aires, Krapf (1955) pointed out that, when he analysed multilingual patients, there always came a time when they involuntarily abandoned the language of their adult life in order to give expression to elemental emotions and infantile attitudes in their mother tongue.

Most of us, in treating patients from alien cultures, will always be denied this degree of understanding, but we can go quite a long way simply by remaining aware of the existence of their very different early emotional experiences, and of the different patterns of fantasy to which these experiences have given rise.

Our Own Society

This is true also, in some degree, of our dealings with patients who come from different subcultures in our own society. Both diagnosis and psychotherapy can be quite severely handicapped by the barriers to communication between a middle-class psychiatrist and a working-class patient This has been demonstrated most clearly by Hollingshead and Redlich (1958), who showed that the treatment accorded to patients attending the same psychiatric clinic was related more closely to the patient's social class than to his mental condition They have documented this statistical finding with telling excerpts from interviews between psychiatrist and patient, which show that neither properly understood the other's language or his different sense of values

That this gulf of incomprehension still exists can partly be laid at the door of psychoanalysis Because Freud's discoveries were made in the course of treating patients from a quite restricted social class, he and some of his followers have tended to over-generalise their theories to include all sorts and conditions of men It may indeed be true that the mental mechanisms are the same in patients from different social groups, but the experiences on which they work may well be significantly different, as Malinowski (1927) pointed out

Freud himself was not unaware of this In a letter to his fiancée written in 1883—long before his first publication in psychopathology—he reflected upon the obvious *differences in life-experience, in behaviour, and in value* between the Austrian intelligentsia and the working classes "I *will* not follow these thoughts further, but one might show how 'das Volk' judges, believes, hopes and works quite otherwise than we do There is a psychology of the common man which is somewhat different from ours" To our loss, he never did return to develop these thoughts further

We need a fuller understanding of the social environment from which our working-class patients come, not merely because it may prove to have some importance in the ætiology of their mental illness—although this has yet to be conclusively established—but more immediately, so that we can make a just evaluation of their symptoms and behaviour

Recently, when reading a paper to the British Sociological Association, I was taken to task for accepting instances of physical assault as an indication of mental disturbance in chronic psychotics living in the community I was asked whether I knew how often wife-beating occurred in the ordinary course of events in the streets in which these patients lived—and I had to admit that I did not know

We must look to the sociologists to make good this gap in our knowledge about our own society, and they are doing so—for example, in the admirable studies emanating from Bethnal Green (Young and Willmott 1957, Townsend 1957) But, until we know enough about their social background to meet them halfway our clinical task in dealing with working-class patients is not unlike that with patients from other, still more unfamiliar, cultures—to take extra pains to overcome the patient's awkwardness in unburdening himself, and to suspend judgment, in our appraisal of his complaints, until we have succeeded, in part at least, in seeing the situation from his point of view

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References continued at foot of next column

GENERAL MEDICAL COUNCIL

In his address at the opening of the Council's 196th session on June 3, Sir David Campbell, the president, said that in recent months steps had been taken towards reciprocal arrangements for registration with two further territories of the Commonwealth On Oct 31, 1957, an Order in Council was made applying part III of the Medical Act, 1956, to Uganda This Order enabled the Council to grant registration to persons holding the licentiateship in medicine and surgery granted by Makerere College On May 7 another Order in Council had been made with reference to Western Australia, where a medical faculty had recently been established in the university It was proposed that the University of Western Australia should begin to grant medical degrees in the latter part of next year, and the question of a visitation of the university on behalf of the Council with a view to recognition of the degrees was being studied At their meeting the next day the Disciplinary Committee would have before them the draft of a new notice to be issued for the guidance of medical practitioners in place of the present "Warning Notice" Since 1914 no alterations of substance had been made in this notice, apart from the inclusion of the new sections in 1916 and 1923 The present notice included no reference to some of the most common or grave offences of members of the medical profession at the present time The committee might feel also that the time had come to discard the somewhat minatory title of "Warning Notice" The part of the new notice dealing with infamous conduct would include a definition by Lord Justice Lopes in 1894 "If a medical man in the pursuit of his profession has done something with regard to it which will be reasonably regarded as disgraceful or dishonourable by his professional brethren of good repute and competency, then it is open to the General Medical Council, if that be shown, to say that he has been guilty of infamous conduct in a professional respect"

"Members of the Council," Sir David concluded, "are not unmindful of the temptations and difficulties which beset members of the profession But our task is to protect the public, and in a difficult case the first question in our minds must always be, 'Is it in the public interest to leave this man on the Register?' Nevertheless, subject always to that primary duty, members of the Disciplinary Committee may, and do, constantly put to themselves the further question 'What is the best thing for the man *himself*?'"

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The Widdicombe File

XLVII ON BEARING FARDELS

DEAR HUGH,

Do you remember writing to me—it must be a year nearly, so fast the time flies—about the Strike and what to think of it? I expect you have long ago forgotten, if not the Strike (and even that is fading) at least your letter, and that I did not reply. You trailed your coat a little, making the most of the arguments for downing scalpels, and obviously expected me to reply at once in my fieriest vein. I did in fact set out to do so, and had covered a page and a half before it became clear that I was stringing platitudes and stale slogans without conviction. I was no longer rock-hard sound on the National Health Service, and even began to find myself speculating irreverently

> Who would fardels bear
> When he himself might his quietus make
> With a small strike-kin?

It shook me to find my faith in the N.H.S. flawed. The N.H.S., or something very like it, was a dream of my youth—a dream compounded in part of highly unpractical Wellsian socialism, and in part of most practical disillusion (as patient and friend of patients, as houseman, and as locum) with private practice as I saw it in Redbrick in the 1930s. It was the kind of dream that was easy to dream in that frustrated decade, when ideals were fashionable only if they were impracticable. Among all the disappointments of the not-so-brave new world we came home to after the war, the N.H.S. seemed so nearly, in broad conception if not in detail (and hang the details, one said, they can be cleaned up later) the fulfilment of those dreams, that it is hardly to be wondered at that I enthused. Within reason, that is: you must not expect very loud fireworks from an academic pathologist. But I resigned from the B.M.A., made myself thoroughly unpopular with the local practitioners by raising the solitary dissentient voice at a meeting to protest about something or other, and might be heard holding forth at all hours to my fellow registrars round the draughty corridors of St. Ethelred's.

Moreover, I did well out of it. It doubled my salary overnight, and has doubled it again since. I was just at the right stage of my career, and perhaps just in the right specialty, to benefit maximally. I had not anticipated this with any exactness: my advocacy of the service was I believe wholly honest—wholly doctrinaire, if you will—but I cannot but admit in retrospect that the accelerated rise of my status and salary did nothing to hasten my disillusion afterwards. (Nor, to be altogether evenhanded, must I fail to admit a suspicion that my doubts coincide with a levelling of the rise of my pay, or that they may even be the onset of that middle-aged shift-to-the-right which afflicts opinions as much as polymorphs.)

Whatever the cause, and I believe it was not wholly intrinsic, I found myself at that moment of truth a year ago, when the Strike seemed imminent, no longer the convinced partisan I had been. I've tried several times, as the months slipped by since, to set down the why's and wherefore's. But each attempt seemed too much a compendium of all the plaintive letters in all the journals in these last years. What can one say new about the dismal registrar muddle, the unbuilt or half-built buildings, the wrongheadedness and boneheadedness of boards, the expense of spirit in a waste of interlocked buck-passing committees—all the infinity of oddments that can be smiled off so easily in detail but add up to so much ill. Let it suffice that for one at least of the service's most wholehearted enthusiasts this rose, like Hassan's, is faded, and this rose is bitter, and this rose is nothing but—the N.H.S.

Not *too* faded, or bitter. Don't let me exaggerate. I still believe in the N.H.S. A return to private practice on any large scale (except as a bludgeon in bargaining) I think would be a far worse catastrophe even than a whole-time salaried service (remind me to discuss with you some time—but it is another story—the subject of the dead hand of Harley Street in the London medical schools). But it seems to me that what began as the great and triumphant embodiment of a noble idea, the one first-class political invention of post-war England, has lived on that *one founding idea* and become *totally* sterile of new ones: that it is in danger of fossilisation into a stone-hard rigid structure that will sooner break than bend to the movements of time.

What's to do about it? Many things, probably; few of them easy to see clearly. But one single thing I believe will be found to lie not very far from the heart of the whole disease—the fact that what is essentially a medical matter is getting more and more out of medical control. Let me expound further.

Have you ever considered, Hugh, how great is the variation in the Parliamentary representation of the various professions? There are some, like the oldest, and the arts generally, and some others that are small or recent or of doubtful professional status, that are not officially represented in Parliament at all. There are others (the Services, Education, and Medicine) which are headed by Ministers, but by Ministers who are never active practitioners in, and rarely have ever belonged to, the professions they control. There are two, the Law and the Church, whose Parliamentary leaders are always leading and active practitioners of their profession, and which carry a number of tied seats in the Upper House. And perhaps for completeness we should include Politics, as the one profession that contrives always to remain its own master in all things.

Let us leave aside the woes of the minor professions, of *the Services* (*it seems to be agreed that we must keep the* troops out of politics) and the teachers (all demagogues fancy themselves pedagogues, anyway) and concentrate on the anomalous position of our own profession. For, as compared with the Church and the Law, it is clearly anomalous. These three are after all *the* three learned professions, very much of a muchness in most people's minds (for good or ill—

"I tell you, Mrs. Hadoway, the clergy live by our sins, the medical faculty by our diseases, and the law gentry by our misfortunes."

"Go not for every grief to the physician, for every quarrel to the lawyer, for every peccadillo to the priest, or every thirst to the pot.")

Let us leave out the archbishops too, lest we import irrelevant emotions, and stick to the comparison between Medicine and the Law. Three posts in every Government are reserved for successful lawyers—the Lord Chancellor, the Attorney-General, and the Solicitor-General. The Chancellor is at once the head of his profession and a Cabinet Minister: an arrangement which looks odd enough, if one chances to look at it with an unprejudiced eye, but which seems to work well enough in practice His is of course a political appointment, but he must be acceptable, in fact if not in the Constitution, to his fellow lawyers as well as to his fellow politicians Beyond these three Ministers, there are the dozen or so English Law Lords with safe seats in the Upper House True, in addition there is the Home Secretary, a layman with a finger in the Law's pie, but he is only the chief of the Law's ancillary services

We, in contrast, have no single smallest seat in any part of Parliament The few doctors in the Lower House have long left behind all active doctoring There are a few medical peers, but few reach that position while they are young enough to do any damage And that's all Nothing seems absurder to the Parliamentary machine than that the Minister of Health should be not, as now, an ambitious politician doing one of his rotating internships in hopes of promotion to a senior job later, but a real live doctor plucked from a thriving practice or popular lectern

Why? Why should we not have a Surgeon-General to run the N H S, helped by a Practitioner-General? And a Lord Great Physician in the Cabinet? And, say, the presidents of the seven Royal Colleges, ex officio, in the House of Lords? It's no less—or no more, if you prefer it that way—reasonable than the Law's quota of offices We matter as much in the world today as the lawyers

Considered soberly, perhaps the two Lower House appointments are not very practical—if only because it's hard to get into the Lower House if you have a proper job to do Perhaps it's not unreasonable to keep a lay Minister of Health, to do the quartermastering, the bricks-and-mortar and ancillary service side of the Health Service What we really need, however, is the medical equivalent of the Lord Chancellor—a Lord Great Physician or whatever you like to call him—a man chosen by the Prime Minister from the leaders of the profession, to have an assured place in the Government, not to run the N H S but to advise on all matters related to the health of the kingdom, and to act as a channel of communication between Government and profession With life peerages so nearly a reality, it is to be hoped that some active members of our profession (and others) will find their way into the Upper House it needs only that one of them be given an accepted status beyond mere membership of the house, and the thing is done

Nonsense, you say? Possibly But I do honestly believe that, now the fate of the profession is so firmly in the hands of the State, no Government will succeed in maintaining happy relations with us till it takes unto itself a colleague who is a doctor—not a politician who was once a doctor—who can talk to both sides from the inside We will not indefinitely tolerate the rule of an administration in which we have no representation

Right at the bottom, in the wards and surgeries and laboratories, we still run our own show As you climb up the hierarchical pyramid to the Minister sitting on the apex, the proportion of laymen rapidly rises, reaching 100% a step or two below the top And the proportion at medium levels, already far too high, is increasing Have you ever noticed how small we bulk in the official publications on the N H S? We forget that we form little more than 10% of its employees The five-day-a-week clerks and porters and boilermen, not to mention the more dedicated ancillaries like nurses and lab-men and physiotherapists, so greatly outnumber us that to the administrators we are an insignificant minority, and a touchy and expensive minority at that, best dispensed with as far as possible Put it at its lowest, we aren't many votes But just as we are in danger of forgetting our numerical insignificance, there's even more danger that the Ministry and all its scattered deputies, absorbed in the renovation of hospital laundries and the pay of spectacle-fitters, will forget that this 10%, in the last analysis, is the one wholly indispensable part of the whole service It's necessary to say, what no-one will say for us, and what we are too apt to understate ourselves, that all the vast and complex structure—wards, clinics, and ambulance services, matrons and mortuary keepers, pharmaceutical firms and Friends of Fairforfechit Cottage Hospital—without us the whole bang lot would be as much use as a chain of medieval lazarhouses

> This is our master, famous, calm and dead,
> Borne on our shoulders

—not very calm and not quite dead yet, but indubitably *borne on our shoulders*

Medicine in the last two hundred years has come into the very forefront of the influences that make a safe life possible to civilised man, and, whatever ideas we may have pinched from other sciences on the way, it is we—a mere half-dozen or so generations of doctors—who have done it And it is still we, and we alone, who can keep it working (Consider, for a moment, to reduce the whole matter to its starkest terms, in whose hands you'd rather be if you had an acute abdomen—two average general practitioners with an old black bag and a kitchen table, or all the non-medically-qualified scientists in the service of the M R C and I C I together, with the best operating-theatre money could buy and the College of Nursing for good measure?) The N H S is no more and no less than a machinery for facilitating the work of its doctors It does no single thing of any value that does not trace back finally to a doctor saying, "Here is a patient of mine this is what must be done if he is to get well and stay well" But we have acquired a colossal administrative tail, a tail that is so large and long and heavy that it begins to think it can wag the dog And that's bad, not only for us but for the whole community whose health is in our hands

There is now a limit of 25% on the medical membership of regional boards It ought to be a minimum of 51% If the present trend continues, the 25% will in time fade to the occasional invited attendance of a single non-voting medical nominee, who will probably be frisked for stethoscopes before he is allowed to enter the boardroom, and made to change his clothes lest he brings the least whiff of the wards or sickroom with him

It is natural enough for the lay administrator to find his medical colleagues difficult The better they are, the more likely are they to have accepted their administrative duties as a disagreeable necessity whose formalities, office hours, and proper channels they treat with improper levity They are insatiably rapacious in their demands for staff and space and equipment, large and airy in their plans, querulous over delays, argumentative to the last degree (among themselves as well as with others), and exceedingly expensive to pay The prospect of any such woolly-headed and extravagant enthusiasts being permitted to run their own show is clearly an administrative nightmare "the country would be bankrupt in a week"

I offer to such the example of the universities The universities are the most successful invention of Western civilisation—indeed, perhaps, its key invention They are of incredible robustness outside the Churches, I can think of only two extant institutions, the British Crown and the Icelandic Thing, that can pretend to any real continuity of life as long as the dozen oldest European universities They are adaptable to all societies the world is full of them now, and the state of its universities is the best test of the civilisation of a country They are nearly always on the verge of bankruptcy—Marlowe knew the truth of it when he wrote

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I offer you a new watchword—No Administration without Representation!

Yours,
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Public Health

Towards Clean Air

Some provisions of the Clean Air Act have been in force for some time [1], and the remainder were brought into force last Sunday, June 1 It is now an offence, punishable by fine, for dark smoke to be emitted from any chimney in England and Wales In a memorandum to local authorities [2] the Ministry of Housing and Local Government points out that measures to reduce smoke will often result in substantial saving of fuel The National Industrial Fuel Efficiency Service surveyed 555 Lancashire boilers and found that installation of economisers and mechanical stokers should raise the efficiency of these boilers to at least 75% of the net calorific value of the coal N I F E S estimated that the expenditure on these modifications would be recouped in about a year by the saving in fuel costs

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[1] See *Lancet* Feb 15, 1958 p 371

[2] Clean Air Act 1956 Memorandum on Industrial Provisions H M Stationery Office. Pp 20 1s

In England Now

A Running Commentary by Peripatetic Correspondents

SINCE our translation to an outpost of Empire we have become steadily more sophisticated, and nothing much surprises us any more True, we have not yet ceased to react pleasurably at the sight of a flock of green parrots sitting on the roof of the physiology department, and the undoubted presence of scorpions in the sand outside anatomy still induces a delightful gooseflesh in our sandalled feet But when a ghastly tumult breaks out over our heads in the middle of a tutorial we no longer turn pale and falter, for we recognise the characteristic sound of possums pursued by the animal-house cat We have grown accustomed to lecturing to dogs of all shapes and sizes, sometimes curled up in the one and ninepennies, and sometimes crouched under the lecturer's bench, ready to spring The other day one of them—a black-and-white spotted affair—got up in the middle of our lecture, yawned widely, and stalked out We did not even blink

Nevertheless our new community lecture theatre has given us pause The room doubles as a histology laboratory, and is therefore long and flat, in contrast to the precipitous cliffside we were wont to confront Indeed, it is only on exceptionally clear days that we can see the back bench from the dais The roof is low and the temperature high, a circumstance dictating the opening of windows which admit the full roar of the heavy traffic and the happy screams of the patrons of the bathing beach outside We have all become hoarse in the attempt to transfer the cargo of our overburdened minds to the keeping of our young friends in the back row, but our biochemist has finally cracked under the strain, and we are waiting for a public address system which will allow us to address the multitude at the cost of fewer petechial hæmorrhages In the meantime our electrophysiologist has kindly rigged us up an imposing assembly of apparatus which subserves roughly the same purpose We have a rickety microphone which we clutch feverishly to our teeth, and our thoughts pass through two black metallic boxes under the bench to a loud-speaker placed on the floor close to the door—an object of keen scrutiny from our canine visitors

In the first box, as in all electronic apparatus we have met, there is a bewildering array of knobs, in this case freely labelled with slogans like "Bass up", "Record", or "Tone", which we take to be Hi-Fi stigmata If we injudiciously leave the microphone to its own devices while we write on the blackboard, it yells and howls till we get back to it again and can twiddle one of the knobs to calm it We are not very good at electrons, but our genial electrophysiologist has given us a thorough coaching on which knob to turn For a time all went well, but our undoing came yesterday, when in the heat of one of our impassioned perorations we arrogantly turned a knob without bending down to make the vital identification Instantly the loudspeaker began to pour forth a stream of abstruse biochemical information, delivered in the voice of our ingenious biochemist and amplified to several thousand decibels

It was not until morning tea that we stopped twitching sufficiently for it to be explained to us slowly and carefully that the *second* black box contained a tape-recorder

* * *

Penny plain or two bucks coloured. I'm green with envy at the Yanks Why should we be stuck to black and white for our passport photographs, while they are allowed to grin at us in glorious 'Technicolor' this year? Our Secretary of State for Foreign Affairs is either getting fuddy-duddy about contemporary British art, or is too allergic to the political implications of the paintbox The best excuse he can give us is that the colours will fade before the passport expires in ten years We work the other way round A glance in the mirror leaves no doubt which of us is fading the faster

If I were not such a shy and modest man, I should say that it would need the genius of a Turner to do full justice to the spectrum in my shaving mirror It presents a worthy chalenough, if one chances to look at it with an unprejudiced eye, but which seems to work well enough in practice His is of course a political appointment, but he must be acceptable, in fact if not in the Constitution, to his fellow lawyers as well as to his fellow politicians Beyond these three Ministers, there are the dozen or so English Law Lords with safe seats in the Upper House True, in addition there is the Home Secretary, a layman with a finger in the Law's pie, but he is only the chief of the Law's ancillary services

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In England Now

A Running Commentary by Peripatetic Correspondents

SINCE our translation to an outpost of Empire we have become steadily more sophisticated, and nothing much surprises us any more. True, we have not yet ceased to react pleasurably at the sight of a flock of green parrots sitting on the roof of the physiology department, and the undoubted presence of scorpions in the sand outside anatomy still induces a delightful gooseflesh in our sandalled feet. But when a ghastly tumult breaks out over our heads in the middle of a tutorial we no longer turn pale and falter, for we recognise the characteristic sound of possums pursued by the animal-house cat. We have grown accustomed to lecturing to dogs of all shapes and sizes, sometimes curled up in the one and ninepennies, and sometimes crouched under the lecturer's bench, ready to spring. The other day one of them—a black-and-white spotted affair—got up in the middle of our lecture, yawned widely, and stalked out. We did not even blink.

Nevertheless our new community lecture theatre has given us pause. The room doubles as a histology laboratory, and is therefore long and flat, in contrast to the precipitous cliffside we were wont to confront. Indeed, it is only on exceptionally clear days that we can see the back bench from the dais. The roof is low and the temperature high, a circumstance dictating the opening of windows which admit the full roar of the heavy traffic and the happy screams of the patrons of the bathing beach outside. We have all become hoarse in the attempt to transfer the cargo of our overburdened minds to the keeping of our young friends in the back row, but our biochemist has finally cracked under the strain, and we are waiting for a public address system which will allow us to address the multitude at the cost of fewer petechial hæmorrhages. In the meantime our electrophysiologist has kindly rigged us up an imposing assembly of apparatus which subserves roughly the same purpose. We have a rickety microphone which we clutch feverishly to our teeth, and our thoughts pass through two black metallic boxes under the bench to a loud-speaker placed on the floor close to the door—an object of keen scrutiny from our canine visitors.

In the first box, as in all electronic apparatus we have met, there is a bewildering array of knobs, in this case freely labelled with slogans like "Bass up", "Record", or "Tone", which we take to be Hi-Fi stigmata. If we injudiciously leave the microphone to its own devices while we write on the blackboard, it yells and howls till we get back to it again and can twiddle one of the knobs to calm it. We are not very good at electrons, but our genial electrophysiologist has given us a thorough coaching on which knob to turn. For a time all went well, but our undoing came yesterday, when in the heat of one of our impassioned perorations we arrogantly turned a knob without bending down to make the vital identification. Instantly the loudspeaker began to pour forth a stream of abstruse biochemical information, delivered in the voice of our ingenious biochemist and amplified to several thousand decibels.

It was not until morning tea that we stopped twitching sufficiently for it to be explained to us slowly and carefully that the *second* black box contained a tape-recorder.

* * *

Penny plain or two bucks coloured. I'm green with envy at the Yanks. Why should we be stuck to black and white for our passport photographs, while they are allowed to grin at us in glorious 'Technicolor' this year? Our Secretary of State for Foreign Affairs is either getting fuddy-duddy about contemporary British art, or is too allergic to the political implications of the paintbox. The best excuse he can give us is that the colours will fade before the passport expires in ten years. We work the other way round. A glance in the mirror leaves no doubt which of us is fading the faster.

If I were not such a shy and modest man, I should say that it would need the genius of a Turner to do full justice to the spectrum in my shaving mirror. It presents a worthy challenge to any manufacturer of colour films, a kaleidoscope of delight to any emigration officer Just imagine the artistic sensitivity of the emulsion to capture that cyanotic tinge in the ear lobes, the turgid pink of nasal mucosa flashing beneath the beacon of acne rosacea, and tell-tale stains of nicotine Hyperpiesia has achieved such a pretty colour gradation down the *venetian blind slats of my treble chins, something* approaching the rainbow lighting of a cinema curtain when the organ goes down A turkey's wattles are hardly a polite *comparison* That telangiectasis across the bridge of the nose is a bit of a blot, but the weight of presbyopia made it an inevitable concomitant of this clonal fading process I do wonder if the new films would bring out the mascara-like subtleties of those drooping suborbital pouches, and record for posterity the silvery current tidemark of an ebbing hair-line

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[1] See *Lancet*, Feb. 15, 1958, p. 371.
[2] Clean Air Act, 1956. Memorandum on Industrial Provisions. H.M. Stationery Office. Pp. 20. 1s.

Yes, we could bring a lot more colour into the drab corridors *of London* Airport and Southampton How the emigration officers would be tempted to linger over their matching cards and lovibond comparators with some glorious pin-up bird of paradise It is time that we British showed our true colours to the world

* * *

" She's my sugar " was a favourite saying when I was a student, and I have always liked the American use of " honey " as a term of endearment How great my pleasure, then, to find these sweet influences seeping into scientific medicine Today I was handed the summary of a report and read " E E G The sugar shows some asymmetry between the two hemispheres but no definite focal lesion or paroxysmal features " Dear girl, bless her heart

* * *

The only place where all departments of our teaching hospital come together is in our colour-slide club For clinical occasions we can rarely persuade a physician to attend a surgical gathering, but once a month we all assemble, peacefully yet critically, to gaze at one another's transparencies Here character comes out and we see our colleagues in their true colours, and it is instructive to note how closely photographic technique mirrors specialist inclination

Our radiologist's habitual underexposures betray the many hours he spends in darkened rooms The surgeons are not surprised that our most investigative-minded physician submits pictures so cluttered with detail that the point is lost The latter might well retort that the indiscriminate tendency of one or two surgeons to lop off heads and limbs reflects their operative hamhandedness It seems most appropriate that the pathologists favour still-lifes Red seems to dominate most slides taken by our blood-and-thunder dentist We also have an endocrinologist who is rather interested in sex reversal, and it is sometimes difficult to recognise his subjects But we all agree *that the radiographers take the best pictures*

* * *

YEHUDI MENUHIN AT THE BATH FESTIVAL

The abbey is filled
The cold surround of funerary plaques
Draws warmth where living listeners
Lean for support against the stiff names of the dead
The body of the church wakes, waiting now to find its soul,
And a stilled torrent of attention
Presses upon one man
So normal, outwardly Everyman, anonymous,
He waits in a lit glade of the choir
Beneath a shadowed forest of fan vaulting
Until the moment calls
The inward person stirs, sketches his signature
In a small, intimate gesture, his face laid close against his instrument,
Then, lost in music, man and violin forget their separate selves
The bow, a slim glint of light, thrusts like a rapier,
The left hand curves in a question mark,
Fingering the unseen
Infinitesimally slender, infinitely tensile,
Heaven and earth are laced together on a single thread of sound

Letters to the Editor

THE RUSSIAN VACCINE

SIR,—The recent publicity given *to the* " Russian vaccine " in the House of Commons and in the Press has already produced a series of anxious inquiries from those afflicted with multiple (disseminated) and other forms of sclerosis I am sure that I am not alone in having had to conduct a number of difficult interviews with patients or with their friends in order to explain what little is known about the vaccine and in order to set out some sort of balance-sheet so that *patients may decide whether or not* to spend the twenty-five pounds for the single course or the seventy-five pounds for *the triple course advocated by* the proponents of the Margulis-Shubladze vaccine

I have been following (by correspondence) the fortunes *of* this particular regime *for* some two years I have approached the problem with a fairly strong negative bias—a bias amplified by the recent report from Belfast by Professor Dick [1] that the vaccine is very largely related to *rabies* The directions which accompany the vaccine also give very little confidence in its efficacy, for the gist *of these* instructions is as follows

An intradermal skin test is carried out If it is negative treatment is carried out subcutaneously If there is a positive skin reaction then it is suggested that an intracutaneous method of treatment should be practised Repetition of the prescribed courses is advised, and it is suggested that on an average it should be repeated once each year The treatment should not be given to well-established cases of disseminated sclerosis but only those in which there are minor and preferably sensory manifestations The appearance of new symptoms is not regarded as a contraindication for the continuation of the treatment The first sentence of the final paragraph of the instructions is eccentrically interesting, for it says baldly " A separate needle is used for each patient " Professor Shubladze is careful to state that the course of injections brings about a cure *of only a third of the number of* patients treated

The American Multiple Sclerosis Society have also investigated the existing evidence about the vaccine, and their opinion is expressed in the following terms

" The fragmentary results of treatment available at present indicate that the vaccine of Margulis-Shubladze is not curative nor does it prevent any exacerbation even while being given "

Further, in January, 1957, Dr F Lhermitte of the *Salpetrière wrote*

" Nous avons en effet utilise le vaccin soviétique dans quelques cas de Sclérose en Plaques Les résultats que nous avons obtenus sont encore trop recents pour que nous puissions porter un jugement définitif, mais ils ne semblent guère encourageants "

On the other side of the balance-sheet the evidence of the alleged efficacy of the treatment comprises the statements which have appeared in the public Press, a series of rumours which are relayed to us by our patients, and the Russian makers' own claim that a third of the patients are cured (It may be mentioned in passing that McAlpine et al [2] state that in 9 out of every 10 patients the disease runs a remitting course in the initial stages) It is, of course, possible that more controlled scientific information already exists in the Russian literature and is as yet undisclosed to us

From the scientific point of view one would have wished that an official statement on this subject could have been made either in the Press or in *Parliament,* but one *has to* recognise that disseminated sclerosis is a condition attended by unique emotional overtones and capable of engendering remarkable pressure groups. Whether we like it scientifically or not a number of patients are going to insist on having courses of the vaccine even at the expense of importing it themselves. Indeed it may well be urged that it is only right that they should be able to choose the way in which they spend their money (though not, of course, on "cures for cancer"). In any case the medical community is going to be drawn into the matter, since the Russian pamphlet on the subject and the official statements insist that the courses of the vaccine should be recommended by doctors and administered by them. It would be more satisfying if we knew that an official double-blind trial were going to be undertaken, but it must be admitted that no prima-facie case can be made out either for the diversion of effort or for the expenditure of the money required. In the event, therefore, it seems very likely that very small groups of patients of quality unselected, except by their determination to try something new, are going to receive somewhat irregular treatment in various parts of the country. No doubt a great deal of psychological, social, and even symptomatic benefit will accrue, but there is only a very slender possibility that real scientific information will be accumulated unless a single rigid criterion is applied to all cases. The assessment and recording of remissions in these circumstances is quite useless. At the risk of being accused of presumptuousness I should like to put forward the notion that all who may be led to administer the vaccine treatment should keep a record solely of the relapse-rate, for this can be the only real criterion of the efficiency of a vaccine treatment. After a period of 5–10 years these figures could either be made available to the Multiple Sclerosis Society or published in the medical Press. The work of Muller[3] and of McAlpine et al[2] already provides an excellent control study of this relapse-rate, and for the purpose of assessment McAlpine's definition of relapse is worth quoting.

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[1] Dick, G W A , McKeown, F , Wilson, D C *Brit med J* Jan 4, 1958, p 7

[2] McAlpine, D , Compston, N D , Lumsden, C E Multiple Sclerosis Edinburgh, 1955

> "The appearance of a new symptom at any time after the initial attack or the return or exacerbation of a previous symptom. A relapse implies either a fresh lesion or the reactivation or extension of an old lesion."

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L. A. LIVERSEDGE

THROMBOSIS OF THE INTERNAL CAROTID ARTERY

SIR,—I much enjoyed the article of May 24 by my friends and former colleagues, Dr Clarke and Mr Harris, on internal-carotid thrombosis simulating intracranial tumour, and they have made a valuable contribution to the clinical evaluation of this difficult and often elusive condition.

At Ashford I have recognised 15 cases of internal-carotid occlusion complete and incomplete in the past three years, and in 3 of these the clinical appearance was that of cerebral tumour, the correct diagnosis being made only after carotid angiography. In 1 of these patients angiography was followed by increase in the aphasic and hemiplegic disability, and with Dr Clarke and Mr Harris I am still concerned about the possible risks of this investigation in carotid occlusion.

While agreeing with them that thromboendarterectomy or operative replacement of the carotid artery may be the treatment of choice, I think they are a little pessimistic about the value and the dangers of anticoagulant drugs in this condition. I have been using these for certain types of cerebral infarction since 1954, and one indication has been where the infarction is associated with carotid occlusion. I consider their value lies in preventing distal embolism from the carotid thrombus and in controlling to some extent the distal propagation of thrombosis as described in Dr Clarke and Mr Harris' second case. My experience has also been that the dangers of intracranial bleeding from anticoagulant therapy after any cerebral infarction is greater in theory than in practice, and my necropsy material has shown no increase in hæmorrhagic infarctions in patients treated with anticoagulants.

I believe that their best use lies in the first stage of the development of the clinical picture when the appearance of focal symptoms is progressive or intermittent.

One of the valuable points that Dr Clarke and Mr Harris make is their emphasis on cerebral œdema in massive infarction of the brain, and they rightly suggest that treatment of this œdema may reduce mortality and morbidity. I have used short courses of corticosteroid therapy intravenously and intramuscularly in this second or acute phase of carotid thrombosis in an attempt to control the response of the cerebral circulation to infarction, but my experience has been too small to assess the value of this method up to now. However, in view of the fact that 1 in every 3 or 4 patients dies from this condition, and half the survivors have a severe and permanent disability, it may be advisable to consider the use of anticoagulants and corticosteroids in those patients considered unsuitable for surgery.

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A. BARHAM CARTER.

CEREBRAL PALSY

SIR,—The letter in your issue of May 3 by Dr Mac Keith and Dr Polani illustrates the difficulty of finding an exact overall definition of infantile cerebral palsy. Throughout the country, many non-medical voluntary bodies are using the word in its widest sense and include all cases of defect of movement due to a cerebral cause. Thus a considerable number of cases that in the past have been labelled crudely as "mental defectives" are now labelled "cerebral palsy" or "spastic".

It is suggested that there are cases of cerebral palsy coming within the precise definition given in the letter that have "certain special motor, intellectual, and emotional difficulties in common and so have certain special therapeutic and educational needs". The definition includes a wide range of cerebral disorders in children, and I would query the statement that they have these specific needs in common. There is a profound difference in the needs of an intellectually normal athetoid with poor ability in the hands and difficulty with walking, and a hemiplegic child with good use of one hand and near normal walking but often suffering from epilepsy and having a lowered intelligence. (May I refute from concrete experience the statement in your leader of April 19 that "it is of little use to train a child to use a limb that he cannot feel"? A hand with marked astereognosis can be used with training and encouragement as a useful assisting hand and give the child an outwardly normal appearance.)

From the Bristol Cerebral Palsy Clinic we have recommended the placement of children in ordinary schools, E.S.N. schools, schools for the deaf and for speech disorders, and for the physically handicapped, occupation centres, mental-deficiency hospitals, for the home teacher service as well as to special units for cerebral-palsied children—some day and some residential, according to need. A few of our children are doing well in ordinary grammar schools. The therapeutic programme also varies from child to child.

From the angle of research, it does not seem desirable to exclude cases that do not come within the definition. I agree with Dr Crawford (May 17) that the term quantitative disorders of movement in mental defectives is misleading. In mental-deficiency hospitals there are cases of abnormal rigidity and bizarre movements, which cannot be called quantitative only For example, there is a case of phenylpyruvic oligophrenia walking in severe equinus, even after bilateral elongation of tendo-Achillis operation There are several members of one family with an identical motor defect, at present ill-defined These cases are on the periphery of the subject, but knowledge can be lost if they are not included Some interesting cases of speech disorder, such as congenital suprabulbar palsy and executive aphasia, could justifiably be included under the heading of cerebral palsy

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[3] Muller, R. *Acta med. scand.* 1949, 133, suppl. 222

There is evidence that some birth-injured cases deteriorate mentally Epilepsy may commence at any age It is doubtful if the use of the words "not progressive" in the definition is clinically exact

There is a need for cerebral-palsy assessment clinics to arrange treatment and education for these children and to do long-term research I feel the title should be loosely interpreted as a "motor defect in children due to a cerebral cause", so that all doubtful and borderline cases can be seen, and in this way precise clinical syndromes and patterns will emerge

Bristol GRACE E WOODS

KETOGENIC ACTION OF HUMAN ANTERIOR PITUITARY IN DIABETIC BABOONS

SIR,—We were much interested in the ketogenic effect of human growth hormone in normal and in diabetic, hypophysectomised subjects, reported by Ikkos et al (April 5)

During the past few years we have been studying various endocrine factors controlling the lipæmia (including cholesterolæmia), ketonæmia, and hyperglycæmia of pancreatectomised, insulin-deprived baboons Removal of the hypophysis from pancreatectomised baboons abolishes the severe lipæmia and prevents the ketosis but does not affect the hyperglycæmia [1] The administration of cortisone to pancreatectomised-hypophysectomised baboons results in the development of a lipæmia even more severe than that in the pancreatectomised baboon before hypophysectomy,[2] but is not associated with a ketosis The administration of acetone-dried human anterior pituitary to pancreatectomised-hypophysectomised baboons intensifies the hyperglycæmia and results in severe ketosis unaccompanied by lipæmia The complete diabetic picture in the pancreatectomised-hypophysectomised baboon can be produced only by the administration of cortisone in conjunction with crude pituitary extract It should be mentioned that crude human anterior pituitary produces severe toxic effects, leading to a high mortality in pancreatectomised-hypophysectomised baboons deprived of insulin In these circumstances the insulin requirements of the baboon are greatly increased The administration of twice the amount of crude human anterior pituitary to normal baboons failed to affect the blood-sugar or to produce a ketosis

It is thus apparent that in the pancreatectomised baboon the lipæmia depends on the degree of functional activity of the adrenal cortex, and the severity of the ketosis is related to the presence of some factor in the anterior lobe of the pituitary and is not determined by the gravity of the lipæmia Our studies show that human anterior pituitary is ketogenic for the pancreatectomised-hypophysectomised baboon no less than it is for the hypophysectomised human diabetic patient

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C GILBERT
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J C ALLAN

DEATH OF A BOXER

SIR,—My own experience of the effect of injury on the brain derives from animal experiments, and it leaves me convinced that very few doctors realise 'how extremely vulnerable the brain is to physical injury In the anæsthetised animal, for instance, once the dura is opened it is practically impossible to touch the surface of the brain without causing sub-pial hæmorrhage at the point of contact and a much more extensive zone of persistent traumatic œdema and ischæmia which must kill thousands of neurones '

If more direct evidence is needed, may I quote from an article by Mr J H Doggart [1] on the impact of boxing on the visual apparatus? Mr Doggart mentions the case of a professional who gave up boxing after a training bout in which he was punched into a mental twilight for three days The boxer is quoted [2] as saying "I wanted to leave the game that had threatened my sanity before I met with an accident in a real fight with six-ounce gloves that would permanently hurt my brain" A weakling, lacking in courage, endurance, skill, character? Unable to stand up and face both physical and moral stresses? Not of the bulldog breed? Well, no—not exactly His name was Tunney and he had twice defeated Jack Dempse

I believe that the end of boxing would be hastened the public were aware of the damage that it causes Fro time to time the individual doctor has tried to do th public service and has failed because the job is too b for any individual May I therefore conclude by repeati my question in a slightly different form? Has any med cal research council, college, society, or other organise body of medical experts ever made any serious attem to marshal the facts about boxing, put them in fro of the public, and keep them there? And if no why not?

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F B BYROM

HOOKWORM AND ANÆMIA

SIR,—The letter of April 19 from Dr Meiklejohn an Dr Passmore on the subject of hookworm anæmia bring timely notice to the need for adequate study of this subjec

The improvement of microchemical techniques, and particu larly the advent of radioactive tracer methods during the las decade, have given a new impetus to the study of the disease

Here, in Malaya, we see a great deal of anæmia and hookworm infection, and we are also fortunate in possessing a tracer laboratory Attempts to study the association between hookworm infection and anæmia are under way, but progress is slow because of the limited man-hours available in a small team

Using ^{51}Cr to estimate blood-loss, I have found, in the eight patients with *Necator americanus* infection studied so far, that the blood-loss was remarkably constant, being about 0 1 ml blood per worm per day, a loss which dropped to a fraction after a vermifuge Two of these patients had losses of over 80 ml of blood each day These losses appear larger than in the twelve patients studied by Roche et al [3] using the same methods Estimations of actual iron losses using ^{59}Fe are under way, as are also the problems of iron absorption

Referring to the possibilities of hæmodilution in severe anæmia with hookworm infection, I have estimated the plasma volume with Evans-blue in ninety-six patients These patients had hæmoglobin levels ranging from normal down to 2 g per 100 ml, the anæmic patients were all suffering from iron deficiency usually associated with hookworm infection, the

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1 Gillman, J, Gilbert, C, Epstein, E, Allan, J C *Experientia, Basle,* 1958, 14 79
2 Gillman, J, Gilbert, C *S Afr J med Sci* 1958, 23, 35

1 Doggart, J H *Arch Ophthal, N Y* 1955, 54, 161
2 Carroll, E J *Amer J med Sci* 1936, 191, 706
3 Roche, M, Perez-Gimenez, M E, Layrisse, M, Prisco, E D *J clin Invest* 1957, 36, 1183

mean blood-volume in those with normal hæmoglobin levels was about 4500 ml, and when the anæmia was severe it dropped to about 2500 ml This diminution of blood-volume was due to a fall in the red-cell volume, the plasma volume remained unchanged.

In my opinion, the study of the anæmia is of secondary importance in hookworm disease, more attention should be paid to such intestinal factors as worm load and the availability, absorption, and losses of iron.

As Dr Meiklejohn and Dr Passmore state, the time is opportune for the organisation of a "properly financed research project" for the study of this disease.

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Federation of Malaya.

P W G TASKER.

POSTMATURITY

SIR,—One cannot adopt Mr Wrigley's plan (May 31, p 1167) for the management of postmaturity on the basis of a low induction-rate or the absence of fœtal deaths due to intracranial trauma With the present conflicting evidence on this subject it is easy to develop an "obstetrical rationale" to suit any plan of management. One must give evidence of an overall reduction in fœtal mortality or a reduction in postmature stillbirths without a comparable rise in stillbirths in induced patients before a plan becomes acceptable

Mr Wrigley admits the variation in fœtal size at one period of gestation, and then uses this as a gauge of maturity In addition, clinical assessment of fœtal size is sometimes inaccurate. One admits the anatomical bogy of a large postmature fœtus which requires careful obstetric management to save its life What, however, is the magnitude of the risk of allowing a large baby to remain in the uterus after the fortieth week of gestation? There is very little growth of the fœtal skull after term, and when the fœtus is large many obstetricians would prefer to keep the membranes intact if cephalopelvic disproportion is possible

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E C. WOOD

INFLUENCE OF LIGHT ON THE HYPERBILIRUBINÆMIA OF INFANTS

SIR,—May I make a few points in connection with the article by Dr Cremer and his colleagues (May 24)?

In 1957 Dr (now Prof) G H Lathe brought to our notice at Queen Charlotte's Maternity Hospital the suggestion by Perryman that sunlight and light-blue fluorescent discharge tubes could reduce bilirubin-levels in vitro and in vivo The team engaged in the study of hyperbilirubinæmia therefore decided to try the effect of exposure to 24-in. light-blue fluorescent 40-watt discharge tubes (G E C.) on a group of babies, mainly prematures, whose bilirubin-levels exceeded 10 mg per 100 ml on the third or fourth days of life.

The time of exposure varied but the bilirubin levels dropped in ten out of twelve cases, the rise in the remaining two being 0 3 and 0 4 mg per 100 ml The change, being less than 2 5 mg per 100 ml. in eleven of the cases, was within the range of experimental error, but the absence of a serious rise in any case looked promising In six out of thirteen controls selected on the same basis as the treated cases there was a rise from 1 mg to 4 2 mg in the comparable period. The team would agree with Dr Cremer and his colleagues that this form of light treatment is probably effective in halting the increase in serum-bilirubin level, although our figures are less convincing, probably because exposure was intermittent We believe that the source of light would have to be greatly strengthened if bilirubin was to be controlled in the presence of active hæmolysis

This work has been dropped for the present for two main reasons firstly, because there is no information about the nature or toxicity of the material elaborated from bilirubin by the action of these light waves, and secondly, because it seems unlikely that the quantitative effect will be great enough to be a substitute for exchange transfusions The treated and untreated cases will be reviewed one year after the last treatment and a short detailed report may then be presented.

Meanwhile, the Queen Charlotte's team feels that the task before them is to improve the technique of exchange transfusion, to try to refine further the indications for treatment both in hæmolytic disease of the newborn and in the very rare cases of prematurity at risk of kernicterus, and to seek methods for hurrying the conjugation of bilirubin into its excretable form

While many workers, clinical, laboratory, and nursing, were involved in this trial, mention must be made of Mr C R J Ruthven, the biochemical technician responsible for the large number of bilirubin estimations required

London, W 6

ALFRED WHITE FRANKLIN

THE NATURAL HISTORY OF CHRONIC BRONCHITIS

SIR,—The points I wish to make about the admirably written paper by Dr Reid and Dr Fairbairn (May 31) are mainly based on a report which I submitted to the heads of my department (the Treasury) in January, 1957, and which is unpublished.

Although this report was not available to Dr Reid and Dr Fairbairn, I had opportunity to discuss some of its contents with them on several occasions In 1947 I attempted, with the help of the late Dr C G Roberts, then chief medical officer to the Post Office, to tackle the problem of chronic bronchitis in postmen, and we discussed the matter with Prof R Christie.

Four years later, when I joined the bronchitis research team of Dr N C Oswald, I decided to leave aside the postmen for the time being, because they form a selected group in which very special factors create problems which do not exist elsewhere. To counterbalance those special circumstances by a control group of non-bronchitic postmen can be fallacious, as is known to doctors who had a large number of postmen under their personal care before the introduction of the National Health Service. Two of those factors I am not at liberty to discuss at present A third—the influence of polluted air on respiratory morbidity—appears certainly correct in that "the acute effects of foggy conditions emerge from the coincidence of onset of bronchitis attacks with thick fog rather than of cold and humidity", but Dr Reid's conclusion that in the London area the "month-to-month changes in incidence [of bronchitis in postmen] are more closely related to changing fog frequency and thus, in a built-up area such as London, to the associated air pollution", I am not willing to concede so simply, because there is a possible source of error in the case of the London postmen. The honest admission by Dr. Reid and Dr Fairbairn ("Although the role of atmospheric pollution in precipitating and aggravating bronchitis may thus be evident, the personal factors involved are still obscure") is caused by the lack of intimate knowledge of how London postmen live and work, which could be acquired before 1948 Such knowledge was the reason why I decided to regard bronchitis in London postmen as a rather special problem, and set it aside for the time being

In my report of January, 1957 (based on the observation of 502 patients clinically and of their sickness-absence records), I came to the conclusion that the sickness record in earlier adult life may have not only *some* (Reid) but also exceptional value in identifying men more likely to develop disabling respiratory disease. In addition, I singled out a group of people who had had a definite history of bronchitis in early childhood, which later seemed to clear up, but recurred after the age of forty Those could be patients whose bronchi had undergone early morbid anatomical changes, as described by Dr Lynne Reid.[1]

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[1] Reid, L. *Lancet*, 195[illegible], i, 275

Finally, Dr Reid's statement, "   since no smoking histories either of 'bronchitics' or controls could be obtained, the role of smoking as a contributory cause of regional and other differences in the natural history of bronchitis cannot be assessed", appears surprising, because in our paper on the effect of cigarette smoking on chronic bronchitis,[2] it was to Dr Reid that Dr Oswald and I gave thanks for assistance in interpreting the statistical aspects The population concerned was 5844 Civil Service clerical workers in the London area, and the conclusion reached was that "the proportion of clerical workers having minor respiratory symptoms and bronchitis was consistently higher in smokers than in non-smokers" Another finding discussed was the strikingly similar prevalence of bronchitis in males and females

London, S W 1 V C MEDVEI

THE BURNING-FEET SYNDROME

SIR,—I read with great interest your annotation of March 8 and Dr Gopalan's letter of April 12 I have observed the burning-feet syndrome in patients with liver disease—subacute viral hepatitis or portal cirrhosis Some of these patients had other signs of vitamin deficiency, such as cheilosis and/or red tongue In none of them was alcohol a contributing factor

The case-histories and morphological findings have been published in detail elsewhere [3] Two patients died from hepatic failure and the spinal cord and peripheral nerves were investigated No pathological changes were seen in the cord Severe changes were found in the small nutrient arteries of the sciatic nerve, however, with thickening of the endothelial layer and narrowing of the lumen, destruction of muscle, cellular infiltration of the adventitia, and granuloma-like formations of adventitial cells (fig 1) The degenerative lesions of the nerve with loss of the medullary sheaths were thought to be secondary to impaired nutrition (fig 2)

These findings seem to confirm Page's opinion [4] that this condition might be due to vascular changes, as suggested by Kinoshita's observations in Japan

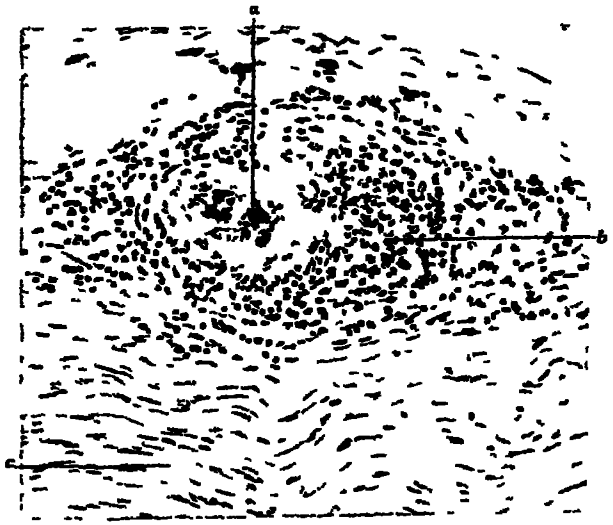

Fig 1—Nutrient artery of sciatic nerve (*a*) lumen nearly obliterated, (*b*) the muscle tissue is destroyed, with cellular infiltration and granuloma-like proliferation of adventitia cells, (*c*) nerve (×80)

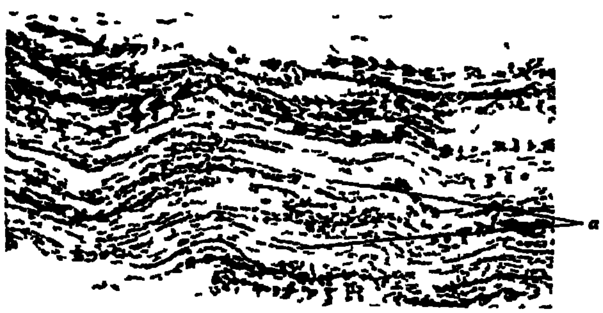

Fig 2—Loss of the medullary sheath, only some normal sheaths remain (*a*) empty endoneural sheaths (×80)

As Dr Gopalan rightly says, the syndrome has several causes It is obvious that once the peripheral nerve is impaired by obliteration of the nutrient arteries vitamin therapy will fail, it was never successful in our cases This may partly explain the therapeutic failure in the series of Bibile et al to which you refer On the other hand, the use of a vasodilator drug, such as nicotinic acid, may be followed by a transient improvement

First Medical Clinic,
Hamburg, Germany G A MARTINI

TREATMENT OF UNDULANT FEVER

SIR,—I have read Dr Lehmann's letter (Feb 8) with great interest, and I wish to make certain points clear

My experience in undulant fever can be divided into three well-defined periods

(1) *1925–42* I saw 637 cases, of which 272 had no special treatment The rest were treated with amidopyrine, neoarsphenamine, gold salts, a formolised extract of *Brucella melitensis* ('Formomelitine'), vaccines and auto-vaccines, or sulphonamides This group is interesting because it provides important data average length of illness, six months, relapses, generally within a month (with no fever) but sometimes after two months, mortality about 6%, incidence of arthritis 8% and of orchitis 12%

(2) 1942–57 I treated 117 patients with antibiotics The figures for most of them are shown in the accompanying table

—	No of cases	Relapses (%)	Cured (%)	Improved (%)	Died (%)	% discharged (month of illness)				
						1st	2nd	3rd	4th	5th
Aureomycin (10–35 g)	77	66	22	71	6	70	13	6	3	1
Chloramphenicol	19	58	37	63	0	63	21	11	5	1
Oxytetracycline plus streptomycin	9	11	56	44	0	78	22	—	—	—

By "cure" I mean disappearance of all symptoms, and by "improvement" persistence of one or more symptoms The results with aureomycin (chlortetracycline) and chloramphenicol were similar, but defervescence was quicker with aureomycin I have treated 3 patients with oxytetracycline alone, 2 with streptomycin alone, and 7 with combinations of various antibiotics, without improving on the figures for aureomycin My best results were with the combination of streptomycin and oxytetracycline, but in none of these cases, except where patients return to hospital, have we known their ultimate condition

Since my article of Jan 25 I have had further experience with 'Cathomycin' (novobiocin), and the results continue to be as I reported

It is most important, however, to know the ultimate fate of the patients who have had novobiocin, and I wrote to the doctors in the villages where patients discharged between fifteen and three months ago are living Of the 36 patients about whom we asked, in 32 there has been no relapse

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2 Oswald, N C, Medvei, V C *ibid* 1955, ii, 843
3 Martini, G A., Kalm, H *Dtsch Z Nervenheilk*, 1951, 166, 17
4 Page, J A *Brit med J* 1946, ii, 260

Two weeks after he went home, 1 of the remaining 4 had a slight febrile illness which recovered at home with no drugs or antibiotics and which was not bacteriologically studied. Another was sent to hospital a month after he was discharged, as he suffered a relapse that was bacteriologically verified. This was again treated with novobiocin with results as satisfactory as in any other febrile patient treated for the first time. He has had no more relapses. The 2 other patients were not known to the doctors to whom we wrote.

Patients who receive no treatment relapse after a period of one or two months, a fact which makes these findings more impressive, as I hope Professor Debono (March 15) will agree.

As to the appearance of rashes, we realise that there can be racial differences in sensitivity to cutaneous exanthems. Their consequences, however, can be greatly mitigated if they are treated adequately. Fortunately, we have had to stop very few treatments, and, even with rashes, we have been able to cure the patient.

It is now wise to wait for the results from a greater number of cases, and I assure Dr Debono that when we have this information we shall record the full details. Meanwhile, our daily increasing experience in acute and chronic cases is strengthening the impression I stated in my article—namely, that novobiocin is the specific drug for the treatment of brucellosis.

Madrid. J. TORRES GOST

"THESE DYING DISEASES"

SIR,—Dr Morrison (May 17) has evidently not understood my letter of April 19, nowhere in that letter do I advocate abolition of the venereal-diseases clinics and dispersion of patients elsewhere. My object was to try and have ready a scheme for the care of these patients if and when the supply of venereologists becomes insufficient for the staffing of the service as at present constituted. It is common knowledge that difficulties already exist in the more remote parts of the country, and one has only to look down the names of the members of the staff of the hospitals in England and Wales to realise that many venereologists have already to cover enormous areas.

The questions raised by Colonel Harrison, Dr Catterall (May 3), Dr Morrison (May 17), Dr Willcox (May 24), and Dr Knight (May 31) are those which need answering constructively. I entirely agree with Colonel Harrison that the present system for treatment of venereal disease can, with very few exceptions, be carried out only by venereologists. Dr Morrison should know that it is because I refused to run the V.D. department in Sheffield on my return from the late war that there is now a consultant venereologist in Sheffield. As a non-venereologist I realised that I was incapable of running an efficient V.D. department on the existing system. It is from this knowledge of the difficulty of working the present system by non-venereologists that I feel that some scheme should be ready for implementation in areas in which posts falling vacant cannot be filled.

If my fears are groundless and recruits of consultant calibre are attracted to venereology, so much the better, and the thought of a helicoptering venereologist serving an enormous number of clinics will be an idle speculation. I do not suggest that the scheme which I put forward is necessarily the best, but at least it would be workable on the existing National Health Service.

Oxford. H. R. VICKERS

TREATMENT OF ASTHMA AND HAYFEVER BY HYPNOSIS

SIR,—Dr Mason and Dr Black (May 24) are concerned at what they consider to be a misinterpretation by me of the method of skin testing employed in their investigation.

They claim that their method of multiple-pressure testing was not a "prick test at all", yet they give an admirable description of the best method of performing a prick test—namely, the introduction of the sharp end of a needle through a drop of extract into the skin, with minimal trauma and yet capable of exciting a reaction. This is the method I employ and advocate for diagnostic testing and which I and others call a prick test. One such prick can and frequently does excite strong reactions, and it is no exaggeration to describe their procedure of ten such pricks on one site as vigorous testing, from which one would expect greater local and systemic after-effects.

I suggested for consideration local "desensitisation" for the loss of sensitivity on the much-tested left arm, and the peripheral vascular effects of hypnosis for the absence of a reaction on the left leg after direct hypnotic suggestion. Discussion of these suggestions would have been more satisfactory if the authors had conducted controlled investigations into local "desensitisation", and into the effects of hypnosis per se and of direct hypnotic suggestion on reactions to allergic and non-specific wealing agents. One would have thought such a control study a basic prerequisite for Dr Mason and Dr Black's study, especially since a single case was involved.

They state that they will be publishing shortly a report on the effects of hypnosis on the tuberculin reaction. There is evidence that peripheral vascular responses can modify tuberculin reactions strikingly.[1] Since such modifications may be paradoxical and complex, depending upon whether antigen, antibody, or inflammatory responses are most involved, care is required in interpreting the results. It is not unexpected that hypnosis may, if only by altering peripheral vascular responses, modify tuberculin reactions, and the examination of skin-biopsy sections from test sites which fail to react under hypnosis may help to provide useful information.

London, W.1. J. PEPYS

PULMONARY MONILIASIS TREATED WITH NYSTATIN AEROSOL

SIR,—Dr McKendrick and Dr Medlock (March 22) report a case of pulmonary moniliasis treated with nystatin aerosol. We have successfully treated a case of pulmonary aspergillosis with inhalation of nystatin.

A farmer, aged 56, was admitted to our clinic in October, 1955, he had had stabbing chest pain for several weeks, and frequent cough with much greenish-grey sputum, he felt weak, had lost weight, and had slightly raised temperatures. Physical examination revealed only a moderate emphysema. The erythrocyte-sedimentation rate (E.S.R.) was 58 mm. in 1 hour. A radiograph revealed calcified residues of a specific apical process and a faint shadow of one fingerbreadth near the upper pole of the left hilum. No tubercle bacilli in the sputum. 2 months later the patient reappeared with complaints of further weight loss, stronger cough and more sputum, stabbing chest pain, and temperature of 38°C for a week. The physical signs and E.S.R. were unchanged. On the radiograph of the chest a three-fingerbreadth shadow appeared in the right mid-zone of indefinite outline and varying density. After treatment with penicillin and streptomycin the temperature fell, but not to normal, the E.S.R. increased to 87 mm., and a chest radiograph revealed an increase of the shadows on both sides. In sputum and bronchoscopic wash-fluid fragments of hyphæ were seen on the direct film and the culture produced

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[1] Pepys, J. *Amer. Rev. Tuberc.* 1955, 71, 49.

Aspergillus fumigatus Treatment with nystatin ('Mycostatin') was started, with daily oral doses of 1 million units The general condition improved somewhat, but the E S R and X-ray appearance did not change After 6 weeks of oral treatment the X-ray shadows were moderately increased, and 2 weeks later a new spotted shadow appeared in the left lower zone The leucocyte-count increased to 12,000–14,000 per c mm In June, 1956, we injected through the bronchoscope 250,000 units of nystatin, in 0 9% saline suspension, into the main bronchi The patient had chills and fever for 3 days, his general condition deteriorated, and the cough increased When the fever subsided we continued to give nystatin by mouth and introduced at the same time treatment by aerosol, thrice daily, beginning with 30,000 units and increasing the dose up to 500,000 units This treatment was given, with interruptions of 1–2 days, for 4 weeks, the general condition of the patient improved, his weight increased, cough and sputum decreased, the temperature became generally normal, and the E S R fell to 29 mm X-ray examination showed a substantial regression of the intensity and extent of the shadows No aspergillus could be grown from the sputum or from the bronchoscopic wash-fluid

After a further 6 months of nystatin treatment the radiograph became clear We attribute the success of the treatment chiefly to the application of nystatin by aerosol Since 1956 the patient has remained in good health and continues to work in his profession

Third Medical Clinic
of the University, Budapest

S GERÓ
J SZÉKELY

VISITING MENTAL HOSPITALS

SIR,—Although the comments of both Miss McClellan and Miss Clarke (*May 31*) are not only true but admirable, they are in no respect a reply to my letter, and, since both appear to have overlooked the only point raised, they unfortunately add nothing towards a solution of this problem My remark concerning visits by *parties* of guildswomen was incidental

It is, therefore, not without significance that both your correspondents lay stress on visits by women's organisations, for this leaves the issue untouched The point is that although *individual persons* are permitted and welcomed to visit our general hospitals for philanthropic purposes, a similar request to visit a mental hospital is invariably turned down

I have written to twenty mental hospitals seeking such permission, and as these twenty applications have met with flat refusals, perhaps Miss McClellan would care to fulfil her desire, and add not only to her happiness but to mine, by introducing me to only *one* medical superintendent in the British Isles who will permit such visits

Edzell, Angus

H G WOODLEY

AN ORAL CONTRACEPTIVE

SIR,—You report (April 19, p 844) a lecture by Dr Gregory Pincus on Fertility Control with Oral Medication Dr Pincus describes experiments made "first in volunteers then in patients in a mental hospital" to assess the ovulation-inhibiting effect of certain compounds, and refers to the indices of ovulation used which included vaginal smears and endometrial biopsies

In 1957 you reported two other American sets of experiments in which mental-hospital patients had been used as guineapigs As I said in my protest[1] about one of these experiments, "this use as guineapigs of chronic psychotic patients who are not able to give or withhold valid permission for experiments in physiological research of this type must be as repugnant to many of your readers as it is to me"

Hawkhead Hospital,
Glasgow

JAMES MILNE

⁂ We have shown Dr Milne's letter to Dr Pincus and his reply follows —ED L

SIR,—Dr Milne's remarks do not seem to me to be particularly applicable to the experiments which we have conducted We reported on the administration of progesterone by mouth to a group of psychotic women and on the administration of a new oral progestin, 17α-ethinyl estra-(5, 10)-eneolone, to a comparable group This experiment was conducted in view of the reported efficacy of progesterone given by injection to women with certain types of psychosis Concomitant observations were made on the physiological effects and the psychiatric state of the patients The physiological observations made would have been impossible without the active and willing cooperation of the patients Furthermore, permission to undertake these observations was obtained from the responsible relatives or guardians of the women patients involved

Worcester Foundation for
Experimental Research,
Shrewsbury, Massachusetts

GREGORY PINCUS

TIME AND THE NERVOUS SYSTEM

SIR,—The definition of a clock given under my name by Dr Gooddy, in your issue of May 31, will be unintelligible to your readers if it is not supplemented by an explanation of what is meant by an A-line If I may be permitted to remedy this deficiency I would explain that an A-line is any unbranched succession of single events, with a first and last term, and such that the first term adjoins the second, the second the third, and so on to the last term One event adjoins another if the end of the former is identical with the beginning of the latter An event is anything which has a beginning and an end in time

According to the definition given by Dr Gooddy a succession of twinges of toothache alternating regularly with smells of onions, all in the experience of one and the same person, would constitute a clock, provided the durations of the twinges and of the smells were all identical But this would be a purely personal clock The clock in the general sense here defined must be distinguished from the pieces of machinery which stand in our halls or on our mantelpieces and are also called clocks These latter are clocks in the above sense *only* when they are *going*

Middlesex Hospital Medical School,
London, W 1

J H WOODGER

Sir JOHN SIMON

MR R J LAMBERT, of Sidney Sussex College, Cambridge, writes

> "In preparing material for a biography I am engaged in a study of the career of Sir John Simon, *successively* (between 1848 and 1876) medical officer to the City of London, the Privy Council, and the Local Government Board He was born in 1816 and died in 1904 I should be most grateful if any of your readers who may possess documents, personal information, or reminiscences concerning him, would be so kind as to contact me"

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[1] *Lancet*, 1957, i, 637

Obituary

ALFRED EDWARD WEBB-JOHNSON

BARON WEBB-JOHNSON OF STOKE-ON-TRENT

Bt, G C V O, C B E, D S O, M B Manc, LL D, F R C S

Alfred Webb-Johnson transformed, successively, the Middlesex Hospital Medical School, the Middlesex Hospital itself, and the Royal College of Surgeons of England He was shrewd in knowing how an institution should develop so as to fulfil its purpose better, he set himself to see that what was needed was done, and he got help and money for his schemes because he could communicate his enthusiasm yet at the same time inspire confidence by his sagacity and sense Transformer rather than reformer, he was not an original thinker, and his talents were no greater than those of many other surgeons But he was an idealist who pursued his ideals with exceptional resolution and exceptional success, and if these ideals were limited they were also important Much of what he built will long stand visible in London, but his greatest service—less tangible—was to reinvigorate his college, which he and his associates since the war have made into a major centre of professional life both for this country and for the Commonwealth

Son of Julia Webb and Samuel Johnson, M D of Queen's University, he was born in 1880 at Stoke-on-Trent, where his father practised and was medical officer of health He did well at Manchester University, winning surgical prizes, and was surgical registrar at the Manchester Royal Infirmary In London he became resident medical officer at the Middlesex Hospital, and in 1911 was elected to the staff He was already in charge of the hospital company of the University of London Officers Training Corps, and in the 1914-18 war he showed his administrative capacity both in command of a hospital and as a consulting surgeon, B E F Returning to civil life as D S O, C B E, and honorary colonel, he entered on six eventful years as dean of his medical school

He was keenly interested in science in general—not merely science as applied to medicine—and he saw that unless the primary departments in a medical school are research departments, in the true sense of the term, medical education must sink to the level of coaching At the Middlesex, by his own efforts, he established a group of professional departments that can hold their own with any university in the country

"One of his particular traits," writes E C D, "was his love of attempting the impossible It was only necessary for some august body to say that such and such a person could not be appointed to a certain position, for various reasons, to stimulate Webb-Johnson to try his strength and come to grips with the authorities This led him into many strange actions, and perhaps the strangest of all—and the one he was fond of referring to—was when he obtained a full professorship in the London University for one of his proteges at the age of 25

"To the end of his days he retained a great interest in young people, and he never lost an opportunity to give them a chance of showing what they were worth Once he had selected a man, he would back him to the fullest extent of his power"

In 1923 he made a tour of hospitals and medical schools in the United States and Canada, and when, two years later, the fabric of the old Middlesex Hospital was found to be unsafe, he was made chairman of the rebuilding committee The slogan "The Middlesex Hospital is Falling Down" appealed to the public, and Webb-Johnson appealed to the men of means whose great benefactions allowed the board to put up the present hospital at a cost of £1¼ million Having done so, the board paid him an unprecedented compliment by naming a ward after him while he could still have his patients in it

His specialty was urology, and he started the urological department at the Middlesex, but he was prepared to undertake any problem in general surgery E W R, his student, his registrar, and later his colleague, writes

"As a teacher he excelled in imparting the fundamentals of surgery, and his ward rounds were popular as well for their intrinsic value to the student as for their amusing comments on the affairs of the day As a chief, he was most generous to his assistants, giving them many chances to practise for themselves what they had learnt from his example His criticisms, though apparently spoken in jest, were always to the point and intended to be taken in earnest As an operator he was quick and dexterous, and in dealing with an emergency he followed the motto of 'quickly in and quicker out' As a doctor he was beloved by all his patients for his unbounded sympathy, ready wit, and unfailing good humour He will be remembered with affectionate loyalty by all who had the privilege of working with and for him"

In 1936 he was knighted Three years later he delivered the Syme oration of the Royal Australasian College of Surgeons, taking them a message from Queen Mary, to whom he was now surgeon-in-ordinary In July, 1941, two months after the partial destruction of the English college by bombs, he assumed its presidency, which he was to hold until 1949—longer than any president before him

Under Webb-Johnson's leadership, the college's disaster became opportunity, and restoration became reconstruction Once again he showed his power to fire others with his faith, and among his vicarious memorials none perhaps expresses that faith so well as the Nuffield residential college of surgery, which opened with its first 25 students just before he left office Other donors, meanwhile, had been led to equip laboratories and endow professorships and departments, by which the college, as a centre of postgraduate education, has enlarged out of knowledge What had been "little more than a rendezvous for examiners and surgical aspirants" became a living organism "alive with youth and enterprise and ambition", in which seniors and juniors meet for informal as well as formal instruction Nor are they surgeons only, for by the end of Webb-Johnson's presidency many smaller bodies were in orbit round the surgical planet Perhaps because this seemed likely to happen to them too, he did not succeed in attracting to Lincoln's Inn Fields the sister colleges which might have formed, with his, the Academy of Medicine which he thought overdue But much integration was nevertheless achieved H S S recalls his own long discussions with the President on how the separating parts of surgery could be kept under one roof

> “ I had suggested the formation of faculties, and he asked me to put down my ideas on paper So one evening in 1941 I went round to take him a draft and we discussed it for a couple of hours during one of the heaviest air-raids of the war! The result was the formation of the first two faculties—Dentistry and Anaesthesia They have been a great success and several similar groups have enabled the college to hold together sections which would have otherwise parted
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> “ Equally important was the co-option to the council of representatives of groups which could not otherwise hope for election—general practice, ophthalmology, obstetrics, dentistry, anaesthesia, and laryngology, if my memory serves me right It was a bold move and a great success ”

Similarly, support and encouragement was given to specialist associations, by providing them, in Lincoln's Inn Fields, with a secretariat and offices for their journals Since 1947, moreover, the college too has had a monthly journal of its own, the *Annals*, which is a link between its far-flung fellows

Webb-Johnson had received a baronetcy in 1945 and he was raised to the peerage in 1948 But, though he had used moderating influence in the crisis over the introduction of the National Health Service, he developed no great taste for debating medicopolitical issues in the House of Lords, preferring always the more direct task In 1950 he became president of the Royal Society of Medicine, then in the throes of adding to its building, and, as usual, he was able to gain the financial support it needed Other duties which he gladly laid on himself were those of president of the Royal Medical Benevolent Fund, and hospitaller of the Order of St John of Jerusalem The many honours which also came to him included the fellowship of the Australasian, American, Edinburgh, and Irish colleges of surgeons, honorary degrees from Liverpool and Toronto, and the highest possible marks of esteem from his own college But, though he enjoyed such recognition—having always given the world at least its due—he avoided pomp, just as he had preferred so often to do his work unobtrusively Like all forceful men, he could be intimidating, but the years emphasised, instead of diminishing, his humanity, and a great many people who knew him will remember him less for his contribution to the surgery of coming generations than for the unexpected fraternity of some casual greeting, for his habit of gentle badinage, or for one of those friendly notes, in his strong and legible script, which were “ Webb-J ’s ” and his alone

Alfred Webb-Johnson married, in 1911, Cecilia Flora, daughter of Douglas Gordon MacRae Lady Webb-Johnson is a member of the court of patrons of the college, as well as its honorary medallist Her MacRae-Webb-Johnson gift to the Hunterian trustees commemorates both her father and her husband

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When I joined the council of the Royal College of Surgeons in July, 1940, Alfred Webb-Johnson was admitted on the same day for his second eight-year period of service At the end of the council meeting he was elected a vice-president, and a year later he reached the presidential chair, although on the council at that time there were several elder statesmen who had served for longer periods It seemed clear that in the crisis which then confronted the college, Webb-Johnson was the “ man of the moment ” During the eight years of his presidency, with others I witnessed his masterly handling of the sequence of events, and was inspired by his vision of what a restored and extended college would mean one day to the prestige of British surgical science It was an unforgettable experience, which was to sustain me when five years later I was unexpectedly called upon to occupy what Webb-Johnson had called the Surgical Woolsack But that was not my first glimpse of this remarkable man in action, for many years before, as surgical registrar at the Manchester Royal Infirmary, he had been one of my teachers At that stage in his career Webb-Johnson was deeply influenced by the intellectual distinction of Mr (afterwards Sir) William Thorburn, whose house-surgeon I was destined to become It was through our common devotion to our brilliant chief that a close bond of friendship was forged between us

Although, after his migration to the Middlesex Hospital, Webb-Johnson became in outward appearance and in his way of life the very model of a London surgeon, throughout his long and distinguished career his attachment to his alma mater remained unshaken As an undergraduate he had been a product of a vintage period which gave to the Manchester medical school a small group of men distinguished later as consultants and teachers—among them Sir William Fletcher Shaw, afterwards president of the Royal College of Obstetricians and Gynæcologists In the company of such men of high ability—and (it is recorded) of high spirits—Webb-Johnson spent his first resident appointment as house-surgeon at the old Manchester Royal Infirmary in Piccadilly It was an experience which provided him with a wealth of anecdotes One which he recounted again and again was of the appearance at the infirmary on a Sunday afternoon of a mysterious stranger, who after enjoying the conversation and hospitality of the residents' common-room, left to take an evening train to London This was none other than Sir William Osler, who later revealed his identity by sending a photograph of himself with an inscription referring to the convivial habits of the residents of the Manchester Royal Infirmary

Until the outbreak of the second world war, Webb-Johnson paid regular visits to Manchester and was an outstanding figure at the reunions of the Manchester Royal Infirmary Old Residents' Club Thus he became known to successive generations of Manchester graduates, who came to feel that in London there was a friend and counsellor to whom they could turn for help and advice Webb-Johnson's undergraduate education and earlier postgraduate training in surgery in a medical school which was an integral part of a civic university—indeed in his day the medical students of Manchester played a dominant role in the social, cultural, and sporting life of Owen's College—gave him a breadth of outlook which became increasingly manifest when he was elected to control the destiny of the Royal College of Surgeons He saw the future of the three Royal Colleges acting in concert—better still, coming together as physical neighbours in the great square of Lincoln's Inn Fields—as an independent and parallel power vis-a-vis the universities in the world of medical education and research This was the essence of his conception of the shape of things to come, and to the Royal College of Surgeons at least he has bequeathed a supreme heritage

H P

In face of his many achievements it is easy to forget that Alfred “ Webb-J ” was an excellent and skilful surgeon, and that the pathway on which he placed his early footsteps, and which was to lead steadily upwards, was indeed a surgical one

I can still remember watching him about half a century ago when he performed his very first operation at Middlesex Hospital and envying the skilful, rapid, and in his hands almost bloodless manner in which he completed a “ Whitehead hæmorrhoidectomy ” He had of course both watched and known Whitehead in his Manchester days

Although in every sense a general surgeon, from the first Webb-Johnson had a penchant towards urology he was one of the first to explore the possibilities of pyelography, and of the purely technical papers which he wrote not a few dealt with urological problems, notably an address to the Manchester Surgical Society on uretero-vaginal fistula which distressing condition he had met 23 times in 23 years

Like many surgeons of olden days as well as modern times his first great experience of surgery was in the service of Mars, and as commanding officer of the world-famous 14 General Hospital at Wimereux in the 1914–18 war, and subsequently as one of the consulting surgeons to the Boulogne base, he was immersed in traumatic surgery In addition he had the opportunity to study first hand and to operate on many patients suffering from surgical complications of typhoid and paratyphoid fevers, and his experience was published first in *The Lancet* (Dec 1, 1917) and subsequently in book form

"Webb-J" was not one of those who essayed novel and daring methods of treatment, but he had plenty of courage when occasion demanded, as when he successfully removed a spleen in an infant two days old for some blood dyscrasia Probably his manifold other interests and the demands on his time did not permit the anxious sleepless nights inseparable from "progressive" surgery The tragedies which he had witnessed in France in the 1914–18 war in the inception of blood-transfusion made an impression on him which remained till the end of his life, and in his surgery he never employed transfusion recklessly and wantonly He was a great friend of Bland-Sutton, from whom he learned the importance of time in surgery

In his early years the influence of Thorburn and the other distinguished neurological workers in Manchester gave him an interest in neurological anatomy, and his illustrations are still to be found in books on anatomy—e g, Treves' *Surgical Applied Anatomy* depicting the fundamentally segmental distribution of the anterior primary divisions of the spinal nerves in the limbs

If the opportunity for service be one of God's greatest gifts to man, "Webb-J" used that gift to the full, but although his skill, the "good doctor" in him, the encouragement that came from his lips, the ready joke, the smile were at the service of each one of his patients, it was rather to suffering humanity as a whole, and to those who minister to alleviate and cure, that he dedicated his great gifts of vision and leadership, and his untiring effort to achieve his object in a worthy cause

G G-T

JAMES WOOD-WILSON

T D, M.D Glasg, D.P H.

Dr Wood-Wilson, county medical officer and principal school medical officer for the West Riding of Yorkshire, died at Wakefield on May 23 after an illness of only a few hours He was 54 years of age

He graduated M B from the University of Glasgow in 1927, and took the D P H three years later After two years as an assistant medical officer at Robroyston Sanatorium, near Glasgow, he joined the staff of the West Riding public-health department in 1932 as an assistant tuberculosis officer He took the M.D the following year, and in 1936 he was appointed an assistant administrative county medical officer with charge of the school and maternity and child-welfare services He had always been an enthusiastic Territorial and in 1939 he held the rank of major in the R.A M C He was at once called up to serve as regimental officer to the 4th battalion of the K O Y L I In 1941 he was released at the request of the West Riding council to take up the post of deputy to the county medical officer He held this appointment till he himself became county medical officer in 1954

Dr Wood-Wilson had much to do with the planning and development of the West Riding scheme for the preventive medical services, and the monthly meetings of the divisional medical officers took place under his chairmanship In 1954 he was largely responsible for the formation of the standing subcommittee on cooperation between medical practitioners and medical officers of the West Riding and he was lately elected chairman of this subcommittee He regularly attended liaison meetings between medical officers of health and the Leeds and Sheffield Regional Hospital Boards

In 1948 he was the captain of the Wakefield golf club and he was often to be found on the golf course in his leisure moments On the reconstitution of the Territorial Army he again became the medical officer to the 4th Battalion K O Y L I, and was awarded the Territorial Decoration and clasp He is survived by his widow, son, and married daughter

A colleague writes Dr Wood-Wilson was an eminent and well-loved member of the public-health service A man of a wide variety of interests, and possessing a very keen intellect, he brought to his work both abundant kindness and sympathy He was tolerant and understanding, with the result that a friendly relationship was built up with all those with whom he came into contact. Of great good humour and limitless patience, he possessed the happy ability of being able to see the other person's point of view His death is mourned by the entire staff in the West Riding health department.

DUNCAN LESLIE FOX

M B Manc, D.P M

Dr Duncan Fox, who had lately been appointed county psychiatrist in Staffordshire, died on May 27 at the age of 33

A brilliant student, he graduated M.B with honours from the University of Manchester in 1948 After holding house-appointments in Manchester at the Royal Infirmary and Crumpsall Hospital he served in the Royal Air Force. In 1954 he took the D P M., and he held posts in psychiatry at Prestwich Hospital, with the Government of Saskatchewan, and in the Manchester region before he took up his present appointment. He leaves a wife and young daughter

N B writes

The ability that made Duncan Fox an outstanding student also characterised his postgraduate career before the onset of his illness There was nothing about his work that was not first-rate and that did not bear the stamp of a fine and exceptional intelligence. Allied to this he had a warm and generous personality that made him beloved by his patients He was a clinician above all else, and in the somewhat dismal world of the mental hospitals in which he worked new entrants to the specialty found his work an inspiration and to him they owe an incalculable debt. He will be missed by many, not least by the countless patients for whom he did so much in those brief years

Appointments

Bloom, H. J G, M.D Lond., M.R.C.P, F.F.R., D.M.R.T consultant radiotherapist, department of radiotherapy, Royal Marsden Hospital, London

Henderson, Dinah C. M, M.D Edin., D M.R.D senior registrar in radiology, The Hospital for Sick Children, Great Ormond Street, and Royal Free Hospital, London

Heron, W C., M.B Belf, D.M.R.D assistant radiologist, Leicester Royal Infirmary and Leicester General Hospital

Hird, Gordon, M.B Aberd, D.P.H M O H. and port M.O, Boston, and assistant county M.O, Holland (Lincs)

Tonge, W L., M.D Manc., D.P.M part-time consultant psychiatrist, Royal Infirmary and Whiteley Wood Clinic, Sheffield.

Birmingham Regional Hospital Board

Bevan, P G, M.B Birm, F.R.C.S consultan surgeon, Birmingham (Dudley Road) group of hospitals

Boyle, J B F, M R.C.S F F.A.R.C.S., D.A. part-time consultant anæsthetist, Wolverhampton group of hospitals

Dencer, Derrick F.R.C.S.E. part-time consultant plastic surgeon, Coventry, Dudley and Stourbridge groups of hospitals.

Hennessy, J D, M.CH N U I, F.R.C.S.E. part-time consultant surgeon, West Bromwich group of hospitals

McDowell, R. F C., M.D Belf., D.M.R.D part-time consultant radiologist, Stafford group of hospitals

Newsholme, G A., M.D Cantab, M.R.C.P, D.M.R.T consultant radiotherapist, United Birmingham Hospitals and Birmingham (Dudley Road) group of hospitals.

Notes and News

PUBLIC-HEALTH DOCTORS' PAY CLAIM

THE Industrial Court has found that a claim for a 5% increase in the salaries of public-health medical officers has not been established The claim covered 2500 doctors and would have cost about £200,000 a year The court said that the doctors must be considered part of the local-authority hierarchy, and, as a claim for local-authority officers from other professions was under consideration, it would " not be appropriate for the salaries of medical officers to be dealt with piecemeal and in isolation while that general claim was outstanding " The award is without prejudice to any claim which the medical officers may put forward when the general claim is settled

WORLD HEALTH ASSEMBLY

THE tenth anniversary commemorative session of the World Health Organisation opened at Minneapolis, Minnesota, on May 26, when Dr Sabih Hassan Al-Wahbi (Iraq), the president, said that W H O 's main task today was to help governments to strengthen their own health services Delegates reviewing progress in their own countries included Dr A da Silva Travassos, who said that malaria had been almost eliminated from continental Portugal, and a regional agreement was being negotiated with Spain for consolidating eradication throughout the Iberian peninsula Pyo Wook Han, Korean Minister in Washington, said that, thanks to international cooperation, there had been only seven cases of smallpox in his country in 1957, compared with more than 43,000 in 1951, 187 cases of typhus, compared with 32,000, and 657 cases of typhoid fever, compared with 81,000 Dr H Kraus (Yugoslavia) predicted that countries which were not now members would soon join W H O , because health problems could be completely solved only on the international level Dr Brock Chisholm (Canada), first director-general of W H O , said that the Organisation had come to be widely recognised for efficiency This was due to the unique character of the Executive Board, whose 18 members act purely as health experts and not as representatives of governments Any attempt to convert the Executive Board into a political body would threaten the future of the Organisation Dr E A Aujaleu (France) said that the various W H O meetings over the past ten years, though not entirely immune to political problems, had attained a remarkable degree of harmony International cooperation would be promoted if people stopped dividing the world into developed and under-developed countries Dr Karl Evang (Norway) said that, owing to lack of funds, W H O was unable to utilise fully the technical knowledge at its disposal Ten years ago the Organisation had hoped to start with a budget of $25 million, but this minimum had not yet been achieved

LONDON SCHOOL OF DENTAL SURGERY

WITH the post-war increase of dental students and the growing needs of research, this school has been finding its share of the buildings of the Royal Dental Hospital on the south side of Leicester Square more and more cramped When Ciro's Club was closed and its premises in Orange Street, immediately behind the hospital, fell vacant, the school authorities acquired the building and received a grant from the University Grants Committee for its purchase, reconstruction, and equipment On June 3 the Queen opened the new extension, which will provide a lecture theatre for 70 students, laboratories, offices, a students' common room, library, and animal rooms

The conversion of a night club into a dental school presented the architect, Mr Douglas Nightingale, F R I B A , with unusual problems To gain more space the main restaurant was floored over at balcony level, and an additional floor erected on the roof Light-weight materials were used so that the building could carry this extra load without expensive alterations In the basement party and external walls were underpinned, and a lecture theatre with tiered seating was then provided by excavation without having to encroach on two floors The theatre has a large projection room, with facilities for storing slides, and a removable bench for demonstrations Operations can be televised while in progress and projected on to a screen in the lecture hall, which also has projection equipment for visual lectures, with facilities for projecting sound on film and with direct intercommunication between the lecturer and projectionist

As the new extension is geographically separate from the hospital a special staff-locating system has been provided and a loudspeaker system with master stations installed Heating and domestic hot water are provided by the hospital's boilers, and wayleave was obtained to bring the pipes through a building which stands between the hospital and the extension As a final example of thrifty improvisation, the spring dance-floor of Ciro's has been resurfaced and now finds a place in the students' common room

CENTRAL HEALTH SERVICES COUNCIL

THE Minister of Health has appointed or reappointed the following doctors to the council and standing advisory committees for the period ending March 31, 1961 New appointments are indicated by an asterisk

Central Health Services Council

Lord Cohen of Birkenhead (chairman), Sir Stanford Cade, Dr Annis Gillie, Prof A J Lewis, Dr Wilfrid Sheldon

Standing Advisory Committees

Medical—*Dr G C Kelly, *Dr Stanley Thomas, Lord Cohen, Sir Stanford Cade, Dr Gillie, Professor Lewis, Dr Sheldon

Dental—Prof M A Rushton, Prof F C Wilkinson

Pharmaceutical—*Dr A M G Campbell

Ophthalmic—*Dr Dorothy Campbell, Mr O G Morgan

Mental Health—*Dr J A Scott, *Dr D H H Thomas, Professor Lewis

Cancer and Radiotherapy—*Mr R D Owen, *Prof D W Smithers, Sir Stanford Cade, Sir Ernest Rock Carling, Lord Cohen, Sir Charles Dodds

Maternity and Midwifery—Prof W C W Nixon

Tuberculosis—Dr P M D'Arcy Hart, Dr Peter Kerley

THE EDUCATION OF THE SCIENTIST

AT the annual meeting of the Manchester Medical Society on May 7, Sir ERIC JAMES, high master of Manchester Grammar School, said that, as regards the specialist education of the scientist, the main point of controversy concerns the degree of specialisation Here there is much confusion, because it is not yet realised that science is an essential part of a liberal education What has to be avoided is not some degree of specialisation at VIth-form level but rather the necessity of a choice of specialism before that stage It is early specialisation, rather than specialisation itself, that is the danger A considerable degree of specialisation at VIth-form level is justified by the inclinations of the pupils, by the educational value of getting to grips with quite difficult work even at an early age, and by the simple fact that if some advanced work is not done at this stage, it must be done at the university It is uneconomic and frustrating, for example, to do premedical science at the university Most important of all, to delay specialisation means much longer university courses, and it is clear that these cannot be contemplated by a country that is having to strain its resources to meet its present needs for university places, even with a short university life

As regards the general education of the scientist, we are faced with a growing responsibility as the number and influence of scientists increases The nature of general education is itself doubtful It is clearly something much more than a body of information and implies the ability to think and discuss value judgments of a kind that do not usually arise in science itself The field is one that is confused by many fallacies—e g , the belief that it is an automatically broadening experience to study any subject that is unrelated to the student's specialist interest We should seek rather for courses which provide stimulus over a wide field—a stimulus that will lead to self-education The fashionable doctrine that " students educate themselves" is also only very partially true The value of residential universities lies partly in the adult guidance that can be given Having regard to the pressure of specialist knowledge and the social background of many of the students, it is difficult to resist the conclusion that the universities must play a more positive part in the general education of their students—e.g , by having arts tutorials for scientists Some of the best American practice is relevant here There can also be little doubt that the general education of our pupils suffers because they are allowed too little leisure, and great efforts will be called for to reduce the factual content of specialist curricula and the pressure of examinations

One thing is clear—that if our education of scientists, whether specialist or general, is to meet the very challenging prospect ahead, much depends on the quality of the individual teacher At the school level, this is the most serious and intractable of all our problems

NEW MALAYAN INSTITUTE OF PREVENTIVE MEDICINE

ON May 14, Sir Robert Scott, H M. Commissioner General for South-East Asia, formally presented the new Institute of Health to Singapore as a gift from the United Kingdom.

The institute houses the department of social medicine and public health of the University of Malaya and the health clinics run by the city council and the Government The staffs of these three authorities will thus join forces within the institute for the teaching and practice of preventive medicine. Dr T A. Lloyd Davies, professor of social medicine, has been appointed coordinator of research.

The building has cost 1¹/₄ million Straits dollars, which has been met by a grant from the Colonial Welfare and Development Fund It stands on land given by the Government of Singapore, valued at $600,000 UNICEF has contributed equipment and W.H.O staff

The clinics held at the institute will include sessions for maternity and child welfare, school and industrial health, dentistry, mass X-rays and B C.G vaccination, ophthalmology, and orthopædics The teaching includes courses for medical students, nurses, health inspectors, and anti-malaria inspectors The students will attend appropriate clinics and the teaching staff will share in running them. The institute stands in a crowded area of Singapore opposite the civil general hospital, and over a million attendances a year are expected

TOXÆMIA IN PREGNANCY

DESPITE efforts to curb that persistent malefactor, toxæmia of pregnancy, it is still contributing substantially to mortality for both mother and child At the first showing on May 30 of a new film, *Toxæmia of Pregnancy*, intended for the instruction of pregnant women, Prof R. J Kellar spoke sorrowfully of failure to reduce the damage done by this disease avoidable contributory causes were often neglected and early signs ignored, so that the power to control the disease by prompt treatment was lost If we were to make an impression on the mortality figures we must pay the closest attention to early signs, patients must be seen more often during pregnancy, and, Professor Kellar urged, prophylactic admission to hospital should be used more freely

The film, which was shown at the London headquarters of the National Birthday Trust Fund, was produced by Dr and Mrs W A. Bullen, with the obstetric advice of Miss Jean Burton-Brown, F R C.S , and sponsored by Pfizer Ltd Skilfully photographed in colour, it points good-humouredly to the dos and don'ts relevant to toxæmia. Mrs Stout, caught during a light snack at the fish-and-chip shop, Mrs Pale, a heavy smoker and inadequate eater, and Mrs Weary, struggling for prodigious hours a day on behalf of her large family, illustrate the don'ts The advice about diet includes the instruction to use salt in cooking but not otherwise The tone of the film seems exactly right for its purpose, and several obstetricians who saw it last week said how much they admired it

The film (16 mm, colour, 17 min) is available on free loan from the Pfizer Film Library, Folkestone, Kent

University of London

The following have passed the final examination for the degrees of M.B , B.S

Honours —Carys M Bannister (*d*), Charing Cross, K. A Barlow (*a*), King's College, M. S Everest (*a*, *c*), St. Mary's, L. J Farrow (*a*), St. Bartholomew's, Edward Friar (*e*), London, J J F Hamblin (*a*, *b*), London, A S Hartt (*e*), St. Thomas's, Margaret E. Hughes (*b*), Middlesex, Sheila M. V Jeffery (*e*), Royal Free, C. F W Palmer (*e*), London, A. W Peck (*a*, *b*, *c University Medal*), Middlesex, Mavis G S Read (*d*), Charing Cross, J J Rippey (*a*), Charing Cross, J G Walker (*a*), Middlesex, J E. C. Wright (*a*), King's College.

(*a*) *Distinguished in pathology*, (*b*) *distinguished in medicine*, (*c*) *distinguished in applied pharmacology and therapeutics*, (*d*) *distinguished in surgery*, (*e*) *distinguished in obstetrics and gynaecology*

Pass —Shirley A P Abell, J F R. Adams, H S O Ahimie, A.-R. M. Al-Adwani, J R. Allan, D J Annal M. V Appa Rao, John Armstrong, J R. Ashwood D H Bailey, W N W Baker, Richard Barker, R. J Barnard R. D S Barnes, Elizabeth S Bates, J T Bavington, J T Beach, R. M Best Elaine M. Binns, Natalie Bogdan, Mary-Ann M Bolt, M. C. Bott, R. D Boyd, Edith J Bradley, J H Bradshaw-Smith, E. S Brawn, J C. Briggs, Peter Brooke, T R. Bull, A G Bundy, D J Burgess, J N Burgess, Shirley F C. Burrell Jean A. Cain J F Cam Moira M. Cameron, Robert Chapple, C A. C. Charlton, J H. Chilman, A. R. O Chinery, R. S Churchill, M. L Clark, Daphne C. K. Clarke Marion Coates, G F Cockings, R. J Cole, A. J Coleman, Janet E. Collinson, V F Collinson, D L. Common Winifred Conn David Cowap, Susanna Cowell, D M A. Cowie, Alan Cox, Sheila M Creegan, Patricia E. Crome, M J Crow, Margaret Crump, C. C. H. Dale, P G Darby, A. H Davies. Ann V Daws, Anne W Deeks. M H de Groot, N A. de Heer, A. M Denman, Nicola A. Dickinson B J Doughty, Jean G Doughty Una M Dugan, M K Dunstan, H D H Eastwood, Janet Y Eccles, John Edmonds-Seal H. J Edwards, D B Ellis, A. J H. Ellison L. A. Emmanuel, Geoffrey Evans, P A Evans, J M. Faccini, Patricia Farren, Margaret G Ferguson, Judith A. G Fletcher, P A Fogarty, C. J Ford Constance E. Fozzard, Ruth Frank, I R. A. Fullagar, P M. Fullman Ramon Gaertner H. A. Garfinkel, James Gekonyo-Mbogo, D W R. George, Valmie Gibbings, Norman Gibbons, Janet L. Gibson, P J Gladders, D H. Glaister, Philip Goldberg, I S Governor, D H Gudgeon Janet M Guenault, J N Guthrie, A. P Hall James Halls Mary R. Hamilton, Sally G Hanson, J T Harries, David Harris, A R. Haste, J S G Hayes, S W Heap, J R. Hearnshaw, Elizabeth M. Hedges, P F Heffron, John Hellewell, Jane V Henderson, Anne V Hickey, D I R. Higton Dennis Hiley, Nitza F Hill Judith Hornung R. G Howard D J Hunt, Anne E H. Jackson, A. G Jacobs H T I James, P W James, Gillian A Jefferies, R. D T Jenkin, G J John G I John, B F Johnson David Johnson, P A Johnson, E. W Jones, G N Jones, J E. Keithley, D H. W Kelly, J H C. Kent, Henry Kerridge-Judd, M. A. R. Kibbler, J O Kilby, K. G Korsah, J R. Lane, F J Le Coulliard, Peter Leftley, Enid S Le Grange, Hilary R. G Lennox, Maxwell Lindsey, Nicholas Lis J P Lissenden, J B Lloyd, O W Lloyd, R. W Lloyd-Davies, Loh Tee Fun, Doreen M Lovern, Martin Lowy, M. J Loxton A. J Lupin C. H. McCleery D R. McCoy, R. F McGann, I A McGlashan C G McKerron, A. D W Maclean, Jean L. McNair, S A. F O McNamara P D Maddocks, Alieh Madjd, A. P Marks. John Martin, A. G F Marus, Josephine Maybanks. M. A. Melsom, Lilianna Melzak, J C. Merrington, P V Mewani, J W Mills, Madjdeddine Mir-Fakhrai, A R. Molyneux, Gillian R. Montague, D T Morris, J E. Morris, P M Morris, F G M G Myer, Michael Myers, C. R. Newman, A. D Noble, P L. Norris, B I Nwakanma O A. Okubadejo, R. L. Owen, Jeremy Parton, G R. Peachey A. J Pechal Norman Peters, B M. Phillips P L. Phillips, Alma T Piesowicz, A J Pim, Elizabeth J Porter, P H Powley, J D Price, B N C. Prichard, Betty L. Priestley, Pamela F Prior, B J Prout, J S Pryor, D J Puddifant, Barbara J Rashbass, Hilary D R. Rendle, John Restall, C. D P Rhodes. Margaret Richardson, Oenone H Roberts P A Robson B A Ross, D F Rowlands, Naomi J Sage A. J Salter, H F G Sewards, Diana R. Shaw, R. F Sheppard, N L. Short. J O Sibthorpe, K. M Simpson, S H. Singh, R. O Skinner, D S Smith, E. O Sofowora B R. Sparke, J D Spencer, P D Sprackling Caryle A. Steen C. G Stephenson, Pamela M. Stracey, Gillian Strube, J R. Sumpton, R. C. Swan M H. Sykes, A. S Tabor, J S T Tallack, D J E. Taylor E. J L. Taylor R. G Taylor, G D Teelucksingh, B M Thomas, E J Thomas J L. E W Thomas, Jill M. Thwaites, R. E. Tonge, Elizabeth A Tooth Bernard Townsley, Rita C. Travers D S Tucker, C. W Venables C. D Venning P J Waight, J W Walker, Sheila J Wallace, G P Walsh-Waring, Pamela Walton, Margaret N Ward M T Ward A. J Welsteed R. G White, Shiona J White, P J Whitfield, Glenwynne Williams, R. P Williams, H D Winnicott, G B Winter, Julia M. Winter, P J Wise R. J Young, Clara Youngday

At a recent examination for the D P M. the following were successful

M. D Eilenberg, Lawrence Goldie, Q A. F R. Grant, W I N Kessel, N B McDiarmid.

University of Liverpool

Dr Thomas Wilson has been appointed senior lecturer in tropical hygiene with effect from April 1, 1959

Increased N H S Contributions

The increases in the weekly contribution to the National Health Service (6*d* for men, 4*d* for women 2*d* for juveniles, 2*d* for employers), which were authorised by the National Health Service Contributions Act 1958, will come into force on July 7

British Spas Federation

On Tuesday, June 10, at 6 P.M at 1, Wimpole Street, London W 1, Prof Howard A. Rusk, chairman of the department of physical medicine and rehabilitation, New York University, will give the Horder lecture. He will speak on crippled people in a troubled world.

Royal College of Obstetricians and Gynæcologists

At a meeting of council held on May 31, with Prof A M Claye, the president, in the chair, the following were elected to council

As representatives of the fellows J H Peel, T N A Jeffcoate, Robert Newton, J F Cunningham

As representatives of the members S D Loxton, J G Gallagher

The following were admitted to the fellowship

Joseph Bamforth, Janet Bottomley, Alexander Buchan, E W C Buckell, T St V Buss, T R Clarke, A G Cumming, A L Deacon, Aileen Dickins, J R Dickinson, G W Garland, E D Y Grasby, Freida Heighway, A F Hobson, R H Horner, Ursula M Lister, Ella A N Macknight, Eleanor M Mills, A A Moncrieff, Chunilal Mukerjee, P D Rajaratnam, E R Rees, Harold Renton, Ednyfed ap Iorwerth Rosser, J K Russell, Appacutty Sinnatamby, R B C Stevenson, D B Stewart, A H C Walker

The following were admitted to the membership

Vijayaratnam Balachandran, Bholanath Banerji, S K Basu, F X Bencini, Olga Bolitho, R T Booth, Carolina A Braga, A F Bushby, A S F Butcher, D P Das, F J de Maria, R E F Devitt, P H Drake, I M Duthie, Mary G Eldridge, Denys V I Fairweather, F G Feinstein, N K Ghose, F R G Gordon, H M Gough, J L Harington, G H Harris, J C Hartgill, C H Hodge, Helena E Hughes, A H John, Satyadev Khanna, Herbert Kramer, Dorothy K C Kwan, C N R Loveys, D J Mackay, Patricia C Mackay, Gillian G Matthews, R J Mitchell, Sukumar Mitra, A K Mukherjee, K D Mullen, Gunaratnam Muttuthamby, Brendan Needham, Jean M North, Joan North, O K Ogan, W H Patterson, P A Rachow, Krishna Sankari, R P Shearman, Bernard Shieff, Ma Khin Si, Devantala Singh, Margaret L Smith, I H F Swain, Mary A T Tolley, R D Upton, B C Uys, A J Van Amerongen, J A Verzin, D W Warrell, James Willocks

Society of Medical Officers of Health

Dr James Stirling, medical officer of health and school medical officer for Chesterfield, has been elected president of this society for 1958–59 in succession to Dr H D Chalke

Family Planning Association

The annual general meeting of this Association will be held today, Saturday, June 7, at 10 A M at Church House, Westminster, S W 1 Sir Russell Brain, the president, will speak at about 11 30 A M

Tritiated Steroids for Medical Research

Small amounts of the following labelled steroids are available through the generosity of the National Research Development Corporation, the Middlesex Hospital Medical School, and the Medical Research Council, for distribution to suitably qualified workers engaged in medical research

Progesterone, corticosterone, aldosterone, cortisol, aldosterone 18–21 diacetate, cortisol 21 monoacetate, corticosterone 21 monoacetate

Workers wishing to use these compounds each of which has a specific activity of 1–3 μC per μg , should apply to the secretary of the Clinical Endocrinology Committee, care of Dr M Gorrill, Medical Research Council, 38, Old Queen Street, S W 1, stating previous experience with tritium measurements and facilities available for the measurements, details of proposed experiments, including quantities required, and when and where the experimental work can start Approved allocations will be free except for a small charge to cover dispensing and transport

A New Voluntary Hospital

The new Victoria Hospital, Kingston, which is the first voluntary hospital to be started since the National Health Service began, was opened on May 21 Speaking at a meeting held in London to mark the occasion, Dr Bernard Lake, chairman of the hospital, recalled that seven years ago the South West Metropolitan Regional Hospital Board had closed the small local general-practitioner hospital serving Kingston and Malden and had turned it into a gynæcological department of Kingston Hospital A fund had at once been opened which had met with a response from all over the world, but it was largely thanks to the subscriptions of local people that it had proved possible to open the new 21-bed hospital The hospital, Dr Lake said, was entirely independent and could not be nationalised except by a fresh Act of Parliament It belonged to the local people, who had direct control through the committee which was elected by the subscribers Patients would be treated free of charge

Prof W J E Jessop and Dr R M Acheson have been elected fellows of Trinity College, Dublin

Dr J M Greenaway, of the University of Sydney, has been appointed as a Roussel fellow to work at King's College Hospital Medical School in the department of chemical pathology on the metabolism of radioactive adrenal steroids

Dr R S F Hennessey, head of the Wellcome Laboratories of Tropical Medicine since 1956, has been appointed to the new post of head of the therapeutic research division of the Wellcome Foundation Ltd Dr L G Goodwin succeeds Dr Hennessey in his former post

Captain J E Stone has retired from his post as director of the division of hospital facilities of King Edward's Hospital Fund for London Mr W E Hall succeeds him.

The address of the Central Midwives Board is now 39, Harrington Gardens, London, S W 7 (telephone Fremantle 4801–3)

At the summer meeting of the Medical Golfing Society, Dr J Park won the *Lancet* cup (scratch medal) and Dr E Canton Seward the Henry Morris cup

Ars Medica, a collection of medical prints made by the Philadelphia Museum of Art in 1952 with a grant from Smith Kline & French Laboratories Ltd , is being shown in London during June at the following places Royal Society of Medicine (June 2–6), Royal College of Surgeons (June 9–11), University College Hospital Medical School (June 12–14), London Clinic (June 15–18), Westminster Medical School (June 18–20), St Mary's Medical School (June 25 and 26)

Diary of the Week

JUNE 8 TO 14

Monday, 9th

University of London
5 30 P M (London Hospital Medical College, Turner Street, E 1) Prof Adrien Albert (Canberra) Chemical Aspects of Selective Toxicity
Postgraduate Medical School of London, Ducane Road, W 12
4 P.M Prof. J S L Browne Unusual Cases in Endocrinology
Institute of Obstetrics and Gynæcology
3 P M (Queen Charlotte's Hospital, Goldhawk Road, W 6) Prof J L Wright (Otago) Breech Delivery

Tuesday, 10th

Royal College of Physicians of London, Pall Mall East, S W 1
5 P M Dr J N Morris Coronary Heart-disease and Occupation (Ernestine Henry lecture)
Royal Society of Medicine
2 30 P M *Psychiatry* (Royal Infirmary, Sheffield, 6) Dr A D Leigh, Dr J W Sandler, Dr Max Hamilton, Dr R H Gosling Methods of Psychosomatic Medicine
Postgraduate Medical School of London
4 P M. Dr E J Zaimis Evaluation of Ganglionic Blocking Drugs
Institute of Dermatology, Lisle Street, W C 2
5 30 P M Dr I A Magnus Urticaria
Institute of Obstetrics and Gynæcology
3 P M (Hammersmith Hospital, Ducane Road, W 12) Professor Wright Vaginal Hysterectomy

Wednesday, 11th

Royal Society of Medicine, 1, Wimpole Street, W 1
4 30 P M *Physical Medicine* Dr M E Fearnley, Dr Michael Kremer Contribution of Physical Medicine to the Management of Multiple Sclerosis
Postgraduate Medical School of London
2 P M Prof L P Garrod Recent Developments in Antibiotic Therapy
Institute of Dermatology
5 30 P M Dr Henry Haber Dyskeratoses
Institute of Obstetrics and Gynæcology
3 P M. (Chelsea Hospital for Women, Dovehouse Street, S W 3) Professor Wright Enterocele
Institute of Diseases of the Chest, Brompton, S W 3
5 P M Mr N R Barrett Idiopathic Mediastinal Fibrosis
Oxford University
5 P M. (Radcliffe Infirmary) Prof John Browne Studies on Adrenal Cortical Function (Litchfield lecture)
Royal College of Surgeons of Edinburgh, Edinburgh, 8
3.30 P M Mr G A G Mitchell Innervation of Blood-vessels (Sir John Struthers lecture.)

Thursday, 12th

Royal Society of Medicine
5 P M *Ophthalmology* Mr E C Zorab, Mr J E H Cogan Erysiphake Extraction of Cataract
Postgraduate Medical School of London
4 P M Dr H E de Wardener Polyuria
Institute of Dermatology
5 30 P M Dr Arthur Tickner Serum Protein Patterns in Skin Disease
Nuffield Orthopædic Centre, Wingfield-Morris Orthopædic Hospital, Oxford
8 30 P M Mr A J Helfet Mechanism, Diagnosis, and Effects of Derangement of the Medial Meniscus of the Knee

Friday, 13th

Postgraduate Medical School of London
10 A M Sir Ralph Marnham *Management of Diverticulitis*
St Mary's Hospital Medical School, Paddington, W 2
5 P M Mr Aleck Bourne Non-Malignant Cervix.
Royal Victoria Hospital, Belfast
4 30 P M (Institute of Clinical Science, Grosvenor Road, Belfast) Prof Howard A Rusk (New York) Dynamic Therapeutics in Chronic Disease (Sir Thomas and Lady Edith Dixon lecture)

Saturday, 14th

Faculty of Anæsthetists of the Royal College of Surgeons of England, Lincoln's Inn Fields, W C 2
10 A.M Scientific meeting on Shock and Allied Phenomena

The Lancet · Saturday 14 June 1958

ENVIRONMENTAL FACTORS IN RESPIRATORY DISEASE [*]

D D Reid
M.D Aberd , Ph D Lond
READER IN EPIDEMIOLOGY AND VITAL STATISTICS,
LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE, LONDON, W C 1

This country has long had an unenviable record in respiratory disease Dr William Farr himself remarked on the rising death-rate from bronchitis and pneumonia during the quickening industrialisation of the 19th century, and now the death-rate from chronic bronchitis among middle-aged men in England and Wales is by far the highest reported in the world If national vital statistics are to be believed, the Englishman between 45 and 64 is, at present death-rates, ten times more likely to die from either bronchitis or pneumonia than, for example, his contemporary in Denmark

Respiratory diseases, either trivial or grave, account for perhaps a third of the total sickness absence in British industry, and, although minor infections herald at least half of the serious infections of the lung, death from these complications is not their only major consequence Every year the examination of national service men re-emphasises the excessive incidence of disabling chronic middle-ear disease in men from the industrial areas of this country—districts already notorious for their high death-rates from bronchitis and pneumonia Voltaire once defended the English adoption of the Muslim practice of smallpox inoculation against the whisper of Christian Europe that the English were mad because "with a gay abandon, they gave their children a certain and dread disease in the hope of preventing an uncertain one" But as a lifetime opponent of laissez-faire, he would have been shocked by our almost complacent ignorance of the malign features of the urban environment which distort the course of respiratory infection to produce crippling and fatal disease

Vital statistics form the coarse sieve in epidemiological studies, sorting out the major factors in the ætiology of disease They clearly show that excessive mortality from respiratory illness is associated with the circumstances of life and work in the poorer parts of our industrial towns This rather vague generalisation has been explained by notions which usually reflect the special interests, the favourite theories, and even the political prejudices of the commentator With varying degrees of justice it has been asserted that more die of respiratory disease in poorer districts because of inadequate diet, less effective medical care, too short convalescence, repeated minor infections contracted in crowded houses, exhausting and dusty work, and life in a heavily polluted atmosphere As Sir George Baker put it in his lecture on the Devonshire colic to this college in 1767

> "A very small acquaintance with the writing of physicians is sufficient to convince us, that much labour and ingenuity has been most unprofitably bestowed on the investigation of remote and obscure causes Such a refinement in theory has, in several instances, been the parent of dangerous errors in practice men are apt to be as partial to their own conceits, as to their own offspring and these opinions seldom fail to govern at the bedside, which have been the result of much contemplation in the closet."

Our ideas about the ætiology of the respiratory disorders must still govern our practice in their treatment and prevention We cannot, therefore, remain satisfied with an impression that environmental factors bulk large as causes of respiratory diseases, such as chronic bronchitis, which are not invariably associated with any particular infecting organism To be effective, disease control must be based on a more precise assessment of the relative importance of each element in the environmental complex and the way in which conditions of life and work are related to the onset and outcome of respiratory illness With Baker, "we have learned not to indulge ourselves in visionary speculations, but to attend closely to nature"

The Home as a Focus of Respiratory Infection

It is natural that we should regard the home and family as the primary unit in epidemiological studies of the common infections of the upper respiratory tract. Some survey work of this kind has already been done In North America Dingle and his colleagues (1953) and Buck (1956) have studied the introduction and spread of colds in suburban middle-class homes In this country Lidwell and Somerville (1951) have surveyed the experience of colds among Wiltshire villagers More recently, Prof Robert Cruickshank, Dr G T Stewart, and I have sought to develop these family studies by combining bacteriological techniques with the traditional methods of clinical epidemiology (Brimblecombe et al 1958) At the same time we have tried to introduce some of the principles of research design now current in experimental medicine into the primarily observational science of epidemiology Our aim was to establish the relevance of certain aspects of the domestic environment of the family to the introduction and spread of these minor infections, which may be the forerunners of chronic respiratory disease

In essence, the ideas are simple The previous studies had established that the age and sex structure of the household, its size, and the presence or absence of a schoolchild, all seemed to affect the family experience of respiratory illness Each of these features of family existence is thus liable to complicate any comparisons made between families living in different conditions such as dampness and overcrowding Yet, if we are to assess the significance of these domestic factors, such comparisons are vital, and they might be obscured or confused by purely coincidental differences in family size or structure

Our primary interest was the effect of domestic overcrowding, and a first essential was thus to ensure that families living in different types of home should be as alike as possible in all other material respects

From among the families of children attending the out-patient department of Paddington Green Children's Hospital were selected all consisting of two parents and three children where one of the children had not yet gone to school From these families were taken only those living in self-contained homes, with no other members of the household, situated within 3 miles of the hospital These homes were then divided, according to our major interest, into groups of differing degrees of overcrowding, thus (*a*) families of five, living in 1–2 rooms were classed as "overcrowded", (*b*) families of five living in 3 rooms were classed as "crowded", and (*c*) families with 4 or more rooms were classed as "uncrowded" These families were then to be observed, by the same team of observers, during the same period At the same time assessments were made of other characteristics, such as degree of dampness of the house, parents' range of human contacts outside the home, and child physique and state of nutrition, which might affect liability to infection

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[*] The first Milroy lecture for 1957, delivered to the Royal College of Physicians of London on February 5, 1957

This was certainly not an experiment, but it was a planned observation, and, as in experiment, the criteria of assessment were crucial Two groups of epidemiological measures were used the first clinical, the other bacteriological Every fortnight the families were visited by a pædiatrician (Dr F Brimblecombe) or a nurse (Miss Dorothy Sanderson) who elicited a careful history of the onset, nature, and course of any respiratory infections in the family during the preceding two weeks Throat and nose swabs were also taken from every member of the family every fortnight The fact that swabs were obtained on 95% of the possible occasions is surely a tribute to their tact and pertinacity

The clinical information was then used to plot the introduction of clinically apparent infection into the family and to track the extent and course of its spread from person to person in the household The summation of many little family outbreaks allowed us to calculate appropriate measures of the epidemic experience of groups of families living in contrasting domestic circumstances In the same way modern techniques of organism typing, applied in this study by Dr Peter Masters and his colleagues, allowed the findings on throat and pernasal swabs to be used to confirm or modify conclusions based on the clinical data The recovery of a type-15 pneumococcus from a family in which that specific organism had not been recently found is treated, by analogy with clinical experience, as a new introduction Its serial appearance in other members of the family can then be used to trace its spread through the household It should be emphasised that, although pneumococci are rather more often recovered from the throat during attacks of coryza, no causal relationship is implied. These type-specific strains are here used simply as readily identified indicators of the familial paths of infection of the nose and throat Their merit lies in the fact that they are more likely to be independent of the differences in susceptibility which may obscure the significance of clinically evident infection

Preliminary sifting of the evidence showed no significant or consistent relation between the frequency of colds and dampness in the home, apparent standards of maternal care, family diet, and the likelihood of extrafamilial contacts But there was a suggestion, based on rather small numbers in the worst group, that the adequacy of the child's clothing for the prevailing climate might be relevant The only technically significant association found was between overcrowding and the incidence of coryza Our concentration on this point thus seems to be justified

To show that overcrowding is apparently important is not enough We need to know, for example, whether the clinical appearances are in fact due to changes in effective contact-rates In other words, we want to determine whether overcrowding increases the frequency and duration of contact intimate enough to allow transfer of infection Alternatively we may ask whether the high attack-rates in overcrowded homes are simply an expression of some other quality of physique or morale, unrelated to the load of infection, of families who live in bad conditions At the same time it would be useful to understand more about the part played by its several members in the introduction and spread of respiratory infections in the family

For these reasons we have summarised our experience in these family epidemics firstly, by calculating clinical measures of introduction and spread The frequency in each crowding group of new cases (i e, cases arising ten days or more after the last previous case in the family) in every 100 weeks of family experience differs little between crowded and uncrowded homes On the other hand, the measure of spread given by the secondary-attack rate—i e, the percentage of those exposed to an index case who show the same syndrome during the ensuing family epidemic—rises consistently from 13·5 to 17·4% with increasing crowding in the home Changes in the ease of spread rather than excessive introduction-rates are thus apparently responsible for the higher attack-rates in crowded homes When the secondary-attack rate is compared with corresponding rates of bacterial transfer (see accompanying table) it becomes quite clear that the clinical appearances are not the result of any lowered threshold of resistance or reporting but a physical effect of the greater transfer of infection in the more crowded homes

CLINICAL AND BACTERIOLOGICAL MEASURES OF TRANSFER OF INFECTION IN DIFFERENT HOUSING CONDITIONS

—	Type of housing		
	Uncrowded	Crowded	Overcrowded
Clinical secondary-attack rate (%)	13·5	16·4	17·4
Bacterial-transfer rate (%)	11·2	13·8	16·0

Family Status in the Introduction and Spread of Family Infections

In the same way, introduction and spread according to the family status—e g, father or pre-school child—of the individual apparently introducing infection into the family can be studied by bacteriological as well as clinical means Fig 1 shows apparent clinical introduction and secondary-attack rates according to the family status It would seem that, on clinical grounds at least, the pre-school child is in these social circumstances the most frequent introducer of new infections The spread following introduction—i e, the secondary-attack rate among the rest of the family—is apparently greatest when the index case is a school child

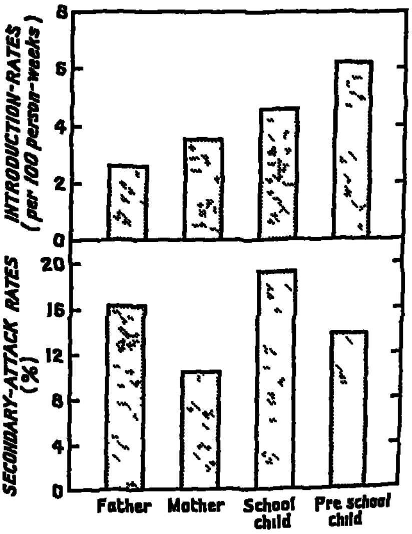

Fig 1—Clinical measures of introduction and spread of respiratory infection by family members

These tentative conclusions must be tempered, however, by realisation that the secondary-attack rates following a father's cold among the remainder of his family are based on the number of attacks among younger and more susceptible individuals The converse holds for the youngest child when colds have to spread against the greater resistance of older people Spread is thus likely to be overestimated for father and underestimated for the youngest child

Some adjustment can be made for this differing susceptibility in those exposed to colds brought in by the various members of the family

The spread following the mother as the index case can be compared with that following a cold in a pre-school child by calculating the secondary-attack rate among the remaining three members of the family (father and the two older children) after each type of exposure In this way the experience of the mother can be used as a standard and each member of the family compared in turn with her Similarly, the susceptibility of, say, mother and child can be compared by the frequency of clinical signs after exposure to colds introduced by the three other members of the family

The interpretation of the clinical data requires some such adjustment for susceptibility If the load of infection encountered outside by the schoolchildren and their younger pre-school siblings were in fact the same, the younger and more susceptible child would be the more likely to appear as the first case in a family epidemic Fig 2 shows that this is in general true, once differences in susceptibility have been taken into account, the introduction-rates become much more alike In short, the chance of bringing home a cold largely depends on personal susceptibility There remains, however, the suggestion that, even in the congested districts round Paddington, the schoolchild is more heavily exposed to infection from outside the home and spreads it within the family much more effectively than anyone else

This conclusion can be tested by comparing, as in fig 3, these clinically determined ratios with the evidence given by the frequency of introduction of new type-specific strains and the rate of their spread from the introducer to the remainder of the family As before, the results for each family member are compared with the mother, but, since the presence of type-specific bacteria in the nasopharynx is being used simply as an indication of mechanical transfer rather than of clinical infection, no correction for immunity has been made Remembering the inevitable crudity of both types of measure, there is an interesting consistency in the pattern, if not in the absolute values, obtained by each approach The bacteriological findings reinforce the slight clinical suggestion of greater exposure outside the home among the schoolchildren They also display an interesting contrast between the experience of mothers and fathers Although organisms new to the family are found more often among the fathers, fathers (because of their higher resistance to infection) appear less often as the introducing case in family epidemics The converse is true for mothers Implicit in this result is the suggestion that the higher incidence of colds among young adult females is an expression of a real increase in susceptibility rather than of any tendency to report minor ailments more easily This result would agree very well with the higher " take " rates among women volunteers in experimental infections at the Common Cold Unit at Salisbury and the higher attack-rates for " colds " in industrial records of sickness absence

Home and School Sources of Throat Infections

On epidemiological grounds the common cold, with running nose and mild fever, could be differentiated from infections presenting with acute sore throats, perhaps with obvious local inflammation, adenitis, and pyrexia With such sore throats not only the seasonal swing but the age-distribution of cases differs from those with coryza The steady fall in the coryza attack-rate from infancy onwards contrasts with the rising " sore throat " attack-rate among the older schoolchildren Bacteriologically there was no very constant association between " sore throat " and the presence of hæmolytic streptococci either in the patient or in the other members of his family at the same time, and it seems likely that more than one organism can be responsible for the clinical syndrome of acute sore throat Nevertheless, there is an agreement between clinical indications and bacteriological results which re-emphasises the importance of the schoolroom as an environment which favours the spread of this particular type of disease of the upper respiratory tract

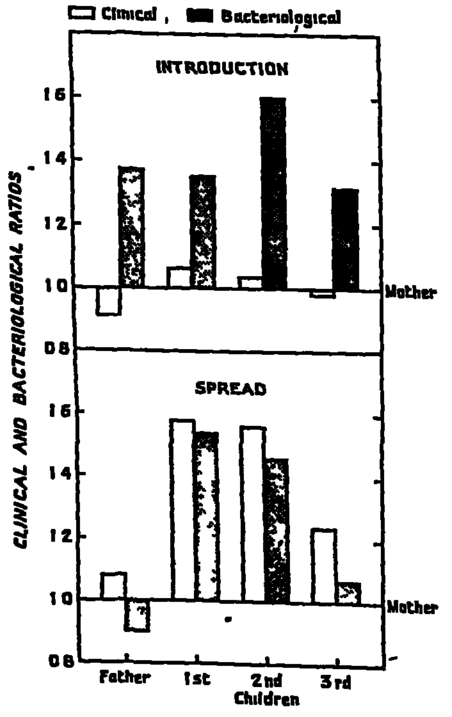

Fig 2—Clinical and bacteriological indices of introduction and spread of infection by family members.

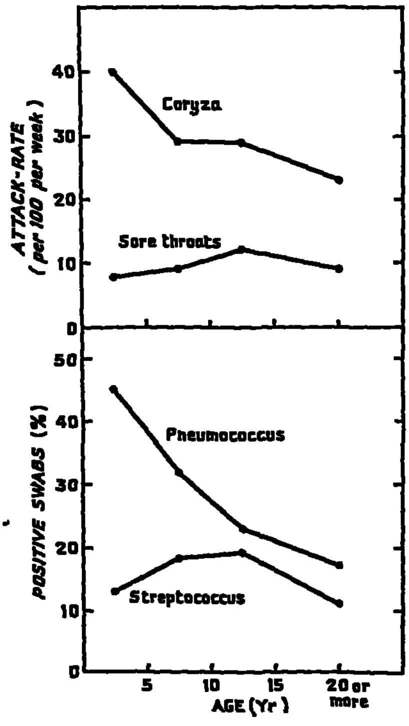

Fig 3—Age-trends in rates of incidence of respiratory infections and bacterial carriage

Although broadly similar, there were intriguing discrepancies between our findings in Paddington and those in other studies both in this country and in North America Our initial impression of the importance of the pre-school child as an introducer of infection to the household contrasts with the American finding of the schoolchild the main culprit Again, while the " coryza " attack-rate among our children dropped steadily from infancy onwards, the rate in the American studies rose to a peak only after the age of 3 It now seems clear that, compared with the sheltered existence of middle-class suburban families in Cleveland or the villagers of Wiltshire, the pre-school child in a congested metropolis is exposed, when at his most susceptible, to a heavier load of infection outside the home And this, when combined with the effect of severe overcrowding within the home, explains a part, but only a part, of the city child's adverse experience of respiratory disease

Spread of Infections in Classrooms

Despite this effect of the urban environment on the incidence of colds among the youngest children, there stands out in all these studies the clear suggestion that, next to the home, the schoolroom may be a principal epidemic focus of colds in the community

The classroom environment may affect the incidence of respiratory disease in two ways—either by affecting the ease of spread or by lowering the individual's resistance to infection Both these possibilities have been studied in some work which also sought to exploit the combined use of bacteriological techniques and clinical epidemiology In this instance, however, the bacteriological data were obtained, not from swabbings of the throat and nose, but by counts of the number of organisms found in samples of air drawn from classrooms in daily use

The history of the development of air-sampling has been recounted by Dr R E O Williams in his 1956 Almroth Wright lecture at St Mary's Hospital

> The notion that counts of bacteria in the air might be useful indicators of the risk of respiratory disease is by no means new In the 1890s, Carnelly et al (1887) tried to relate the number of organisms settling on agar plates in the overcrowded houses of the poorer parts of Dundee to the mortality from respiratory disease in the same districts at that time With commendable courage they visited Dundee homes between midnight and four in the morning to expose plates in rooms where up to eight people might be sleeping (*Only once, they assert, were they received uncivilly*) It was perhaps hardly surprising that they were able to show that the number of organisms of all kinds found in the air was seven times higher and the mortality appreciably greater in one-roomed houses than in four-roomed houses in Dundee at that time These workers could not and did not claim that they had demonstrated any very direct cause-and-effect relationship Very little has been done since then to test the practical validity of air-sampling as a measure of air hygiene—i e, an index of the risk of the airborne spread of disease in occupied spaces
>
> During the earlier part of this century, interest in the possibility of any widespread aerial dissemination of infection languished The work of Flugge (1897), for example, appeared to show that infected droplets emitted from the nose and throat of a patient by speaking or coughing were carried only a yard or so from the patient's mouth Again, since no tubercle bacilli were recovered from the air of rooms inhabited by patients with that disease, this too seemed to dispose of the idea that respiratory infections could be effectively spread by widely circulating infective droplets in wards or other occupied rooms
>
> In the 1930s, however, Wells (1933) introduced more efficient methods of sampling the bacteria suspended in room air and showed quite conclusively that organisms could be recovered from the air at considerable distances from their human source It appeared that these organisms were projected from the mouth in droplets of moisture which became lighter as the moisture evaporated and were carried on air-currents quite widely across the room Only the larger and heavier droplets fell almost at once to the floor But, as Williams pointed out, these were the only droplets effectively caught on the plates used by Flugge as a sampling mechanism Flugge's restricted views on the feasibility of infection being spread in widely disseminated nuclei thus stemmed from a limitation imposed by his own technique
>
> At this stage it would be a gratifying exercise for a teacher of epidemiology in the older fashion to point out how neglect of the simpler methods of direct field observation had stultified progress Unfortunately, the whole burden of field inquiries during this century led Stallybrass to remark in 1931 "Gone are the conceptions of the miasmas, the malarias, the pythogenic or filth originating diseases in their original meanings and with the miasmatic theory has gone the general conception of air-borne infection " Experience in the infectious disease hospitals certainly accumulated to show that measures to limit transmission by fairly close contact were enough to prevent serious cross-infection (Harries 1935)
>
> But some fragments of epidemiological evidence obstinately remained to suggest the possibility of airborne spread of infection Stallybrass himself quotes a suggestive experience reported by the U S Public Health Service during the 1918 influenza epidemic A prisoner from a distant town entered an American prison on an evening when a concert was being held there He failed to report sick but went to the concert instead His movements, seating, and contacts were, inevitably, both strictly prescribed and well known Yet he infected several other prisoners in the room seated at distances far beyond the range of Flugge droplets Observations like these gave fresh interest to the work of Wells on widely floating particles ejected from patients' mouths as a source of epidemic infections Wells et al (1942) also claimed to have reduced the incidence of specific infections in schools by using germicidal ultraviolet-ray screens in classrooms to prevent the wide dissemination of infection from an affected child

Experiment in Air Hygiene in Schools

These were important findings and the Air Hygiene Committee of the Medical Research Council (1954) set up a large field trial to see whether, in primary schools of the compact London suburb of Southall, these results could be repeated The experimental plan was quite simple

> In three Southall primary schools, ultraviolet-ray lamps were installed in classrooms, assembly halls, and cloakrooms so that their rays, projected upwards to the ceiling, formed a bactericidal barrier through which infected droplets would have to pass in the normal course of room ventilation Such an arrangement could have no effect on direct contagion In three other Southall schools, whose past experience of infectious disease had been similar, no ultraviolet-ray lamps were fitted, but precisely the same observations were made there during the three years of this field trial These observations included complete recording of the sickness experience of all the pupils in these schools Regular visits were also made to randomly selected classrooms in every school Samples were drawn from the air by the slit-sampler developed by Dr O M Lidwell, and a note was made of those characteristics of the classroom environment (such as indoor temperature, relative humidity, and ventilation) which might have some effect on the incidence and airborne transfer of infection At the same time assessments were made—on a rather subjective basis—of the amount of talking and activity of the class, since both these aspects of class behaviour are likely to increase the bacterial content of the air

This field trial aimed at determining whether the interruption of the aerial routes of transfer by the bactericidal ultraviolet rays would result in any general lowering in the incidence of the presumably airborne respiratory infections or a *fall in the cross-infection* rates within classrooms of the specific infectious illness such as measles and chickenpox But as a useful by-product of this investigation Dr Robert Williams, Dr Owen Lidwell, and I were interested in the prospect of finding out whether the bacterial counts in samples of air in classrooms could be used as an index of the risk of cross-infection among the children there Two kinds of media were used in the slit-sampler, the first was a selective medium which allowed colonies of *Streptococcus salivarius* to be recognised and counted with ease, the other was serum-agar, which, being non-selective, allowed a " general flora " count of all kinds of organisms in the sample of air

Sickness experience was measured in two ways For measles it was possible to plot the course of classroom epidemics from the date of onset of absence of the first or index case to the wave of secondary cases between the 7th and 16th day thereafter The secondary-attack rate among those pupils who had never had measles before could thus be used to measure the risk of transfer For the non-specific upper-respiratory-tract infections no such precise measure of transfer risk was practicable The crude incidence-rates had to be used instead

These measures of sickness were accumulated over the school year for a particular classroom and then related to the average of the readings of temperature, ventilation, or bacterial counts made in that room at intervals throughout the school year The basic assumption is that the teacher in charge is fairly consistent in her standards of suitable room temperature and class behaviour Unfortunately, from the point of view of analysis, the most talkative classes tend to be at once the most active, the youngest, and the most susceptible Some preliminary analyses showed that the *Streptococcus salivarius* was more closely related to talking, while the " general flora " count seemed to be a better index of the amount of air pollution by activities which disturbed secondary reservoirs of infection on clothes or in floor dust Statistical techniques of partial correlation analysis are, therefore, required to allow, for example, for the fact that warmer rooms tend to have a lower " colds " incidence and lower measles secondary-attack rates

Despite these complexities, we found that there was a significant relation between the *Strep salivarius* count and the measure of transfer of measles infection in the classrooms given by the secondary-attack rate (fig 4), and this relation was not materially affected by adjustments for simultaneous variations in the classroom environment or pupil behaviour

On the other hand we could demonstrate no significant relationship between the incidence of colds and the corresponding *Strep salivarius* counts There was, however, a clear suggestion that the incidence of these disorders was related to the general flora count in the same classroom

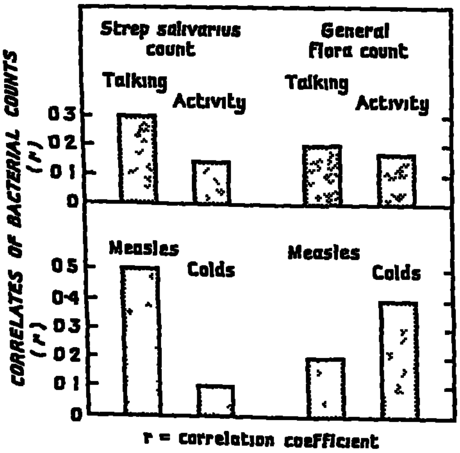

Fig 4—Net correlation of air counts of bacteria in air with classroom behaviour of schoolchildren and incidence of measles and colds

Two suggestions emerge from these results Widespread aerial dissemination of infective droplets is apparently important in the spread of measles On the other hand, the more direct transfer produced either by physical contacts, droplet spray at close range, or activity stirring up secondary reservoirs of infection in clothes or dust is the more likely mode of spread of colds in classrooms When the results of the main trial itself are reviewed, they certainly appear to be consistent with these hypotheses The ultraviolet irradiation produced both a large decrease in the counts of *Strep salivarius*, which were used as indicators of widespread air pollution from the respiratory tract, and some reduction in the incidence of measles But the bactericidal barrier against long-range transfer of infected droplet nuclei had little effect either on the counts of general flora, dispersed by activities likely to favour more immediate contagion, or on the incidence of the common cold

Some Practical Conclusions

Lord Macaulay once said that " Facts are the mere dross of history It is from the abstract truth which interpenetrates them, and lies latent among them like gold in the ore, that the mass derives its whole value " But to extract the absolute truth in a science like epidemiology, based on observation rather than experiment, is much less easy than Macaulay makes it sound Certainly neither bacteriological investigations nor clinical field studies can claim any monopoly as paths to the ultimate secrets of the epidemiology of the common cold But, used together, they hold out some hope of discovering the common thread that explains the pattern of assembled facts Bacteriological opinion may have swung too violently from a denial of the possibility of any wide airborne spread of disease to an overestimate of its potential importance in the ubiquitous upper-respiratory-tract infections Clinical studies, conducted in parallel, have led to a more balanced assessment On the other hand, the results of clinical inquiries may be obscured by wide differences in resistance, bacteriological findings have then clarified the route of infection in family outbreaks of respiratory disease Agreement between clinical and bacteriological results brings added confidence, and in these combined studies they do show that passage of colds apparently depends much more on the direct and intimate contact of overcrowded homes or noisy classrooms full of active children than on any widespread dissemination of droplet spray

The late President Roosevelt was reputedly fond of saying that " Politics is the science of the possible ", and the same principle of limiting anticipated ends within available means applies equally to preventive medicine Hopes for the control of the common cold rest on the belief that the aerial transfer of infection can be effectively blocked The work now reported leads, I fear, to a more tempered view

In the Royal Air Force, Air Commodore T C Macdonald and his colleagues (1955) have shown that what might be termed " blunderbuss " measures designed to block all possible aerial routes of spread by ultraviolet lamps, oiled floors, and screens between beds have had no effect on the incidence of upper-respiratory-tract infection in Service barracks The failure of such attempts to prevent epidemics of colds in communities could be explained if ubiquitous cold virus infection appears clinically in a seasoned population only after exposure to large doses at close range

My aim is to preach, not nihilism, but realism, for there are likely to be many environments—as in the medical laboratory, the postmortem room, or the operating-theatre—where quite small doses of airborne organisms may infect susceptible individuals at long range Here there is immediate scope for more research by the combined approach on the practice of air hygiene, but it is hard to be sanguine about its value against the common cold

(*The references will appear at the end of the second lecture*)

GASTRECTOMY AND LOSS OF WEIGHT

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Low body-weight is common in patients who have had operations on the stomach It may represent loss of weight after operation or failure to regain completely weight which had been lost before It often causes concern to the patient, and may prevent him from doing heavy work (Moroney 1953) It is occasionally associated with pulmonary tuberculosis (Pulvertaft 1952, Pearson 1954)

Many of the factors that influence the weight-loss are well-known It is related to the extent of the resection, being greatest in those who have lost the whole stomach (Zollinger and Ellison 1954) It is also influenced by the type of the anastomosis A Billroth-I gastrectomy causes less loss of weight than a Polya (Moloney 1954, Wollaeger 1950), and probably less than simple vagotomy and gastroenterostomy (Zollinger and Ellison 1954) Women are more prone to be underweight than men (Blake and Rechnitzer 1953, Anderson et al 1955)

There are two known causes of low weight

(1) A reduced intake of food may be the result of a poor appetite, a reduced capacity, or postcibal symptoms This is probably the main cause, but little is known of its quantitative aspects

(2) There is often an increased loss of food derivatives, particularly fat and nitrogen, in the fæces It is rarely great enough to influence body-weight significantly except in those who have undergone total or near-total gastrectomy

Some patients remain underweight even when they appear to be eating enough and not to be losing an excess of calorific material in their fæces

Various forms of treatment, designed to improve weight, have met with varying success

The intake of food can be increased by giving small, frequent feeds with a high calorific value and low bulk A slight gain in weight may follow (Brain and Stammers 1951, Ellison 1955, Lepore 1956)

Attempts to increase the absorption of fat and nitrogen by feeding pancreatic extract, bile salts, or emulsifying agents have produced no beneficial effect (Ward-McQuaid 1949, Ellison 1955)

Operations which relieve postcibal symptoms (conversion to Billroth-I or Roux-en-Y anastomosis, &c) often cause a striking gain in weight (Perman 1951, Capper and Welbourn 1955)

Testosterone, given to patients who are underweight after total gastrectomy, improves appetite and food intake (Van Wayjen 1957), but its effects on body-weight are not known

The present investigation has three parts The first is concerned with some further factors which influence body-weight after gastrectomy The second is a quantitative study of the relation between food intake, postcibal symptoms, and body-weight The third is a controlled trial of various methods of increasing the weight of those who have lost it The first two were made by one of us (Welbourn 1953) some years ago in the department of surgery, Liverpool University

Factors Influencing Body-weight

209 patients who had undergone gastrectomy of various types were studied

There were 174 men and 35 women 170 had had subtotal (three-quarters) resection, with a Polya-Finsterer anastomosis, for peptic ulcer A few had had less radical resections with the same (16) or a Billroth-I (9) anastomosis Some had undergone œsophagogastrectomy (8) or total gastrectomy (6) for carcinoma of the œsophagus or stomach or for benign lesions

The patients fell into two groups of approximately equal size Those in the first had had their operations one to five years previously, and those in the second six to fifteen years previously In all cases the patient's own estimate of health weight (i e, his weight before development of the lesion which led to operation) was recorded The weight at the time of operation was obtained from the case-sheet and the weight at the time of follow-up was measured

Simple inspection of the data revealed that, on the whole, those who had lost much weight before operation tended to regain it after, while those who had maintained weight and the few who had gained weight up to the time of operation tended to lose it afterwards This point was investigated further by comparing the relation between the preoperative and the postoperative changes in weight for all the patients (fig 1) The correlation between the two was highly significant ($P < 0\ 001$) The middle sloping line on the graph represents the regression of the postoperative change (y) on the preoperative change (x) That is, it shows how, on the average, y is influenced by x The two outer sloping lines are drawn at two standard deviations from the regression line, so that they contain

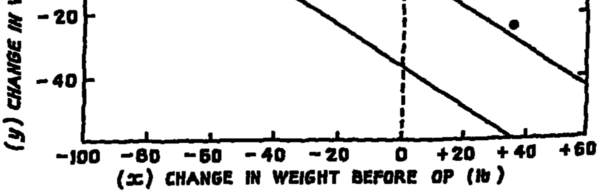

Fig 1—Weight changes before and after gastrectomy Average postoperative change for given preoperative change

x, change in weight before operation in lb (i e, preoperative weight minus health weight)

y, change in weight after operation in lb (i e, postoperative weight minus preoperative weight)

$r_{xy} = -0\ 67$ $P < 0\ 001$ $\hat{y} = -0\ 656x - 5\ 445$ $s_{y\,x} = 15\ 55$

= mean $\bar{y}$ for given arrays of x

Middle sloping line = regression of y on x

Outer sloping lines = $\pm 2s_{y\,x}$

between them about 95% of the observations Inspection of this graph shows, for instance, that on the average a patient who loses 80 lb before operation ($x=-80$) gains 47 lb afterwards ($y=+47$), one whose weight does not change before ($x=0$) loses 6 lb after ($y=-6$), and one who gains 20 lb before ($x=+20$) loses 19 lb after operation ($y=-19$)

This finding can be illustrated in another way The 170 patients who underwent subtotal gastrectomy with a Polya-Finsterer anastomosis for peptic ulcer can be divided arbitrarily into three groups on the basis of the preoperative change in weight (fig 2) Group A (57% of the patients) remained within 15 lb of their health weight up to the time of operation, on the average they lost 3 lb before operation and another 4–6 lb afterwards Group B (42%) lost 15 lb or more before operation, their average loss being 35 lb After operation they *gained* an average of 20 lb, but remained a little lighter than those in group A. The average weights of those in groups A and B who were seen one to five years after operation were almost identical with those seen six to fifteen years after This indicates that, although the weight changes rapidly in the first year after operation, it alters very little later Group C (1%) *gained* 15 lb or more before operation, their average gain being 43 lb After operation they lost 20 lb but remained well above their health weight.

Although we have not presented the results for the two sexes separately, our data confirm that women tend to be relatively more underweight than men both before operation and at all periods after

Food Intake, Postcibal Symptoms, and Body-weight

Two groups of 15 patients, who had undergone subtotal gastrectomy for peptic ulcer at least a year previously, were investigated Those in group I ("normal weight") had gained weight since operation and weighed at least as much as they did in health. Group II ("low weight") had lost 15 lb or more since operation and were, on the average, 29 lb below health weight The average daily consumption of food was estimated by obtaining from each patient a complete list of what he had eaten during one week and discussing it with him The composition of the food was calculated from standard tables (McCance and Widdowson 1946) Each patient's requirement of calories was estimated by questioning him about his occupation and habits and assigning him to one of seven "degrees of activity" (British Medical Association 1950) The severity of any postcibal symptoms from which he suffered was also assessed

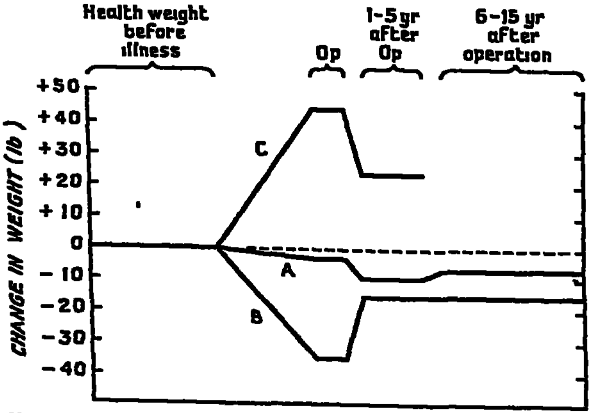

Fig 2—Effect of subtotal gastrectomy on body-weight. Mean weight in relation to health weight, at various periods, in three groups of patients.

A, within 15 lb of health weight up to the time of operation B, lost 15 lb or more before operation C, gained 15 lb or more before operation

TABLE I—INTAKE OF CALORIES AND PROTEIN AND INCIDENCE OF POSTCIBAL SYMPTOMS IN RELATION TO BODY-WEIGHT AFTER GASTRECTOMY (14 PATIENTS IN EACH GROUP)

—	Normal weight	Low weight
Calories		
Mean daily intake		
Actual	2955	1910
Required	2910	2535
Actual intake as proportion (%) of theoretical requirement	102 (S.D 31)*	76 (S.D 20)*
Protein		
Mean daily intake (g)	73	55
Mean proportion (%) of calories provided by protein		
Actual calories	10	12
Required "	10	9
Postcibal symptoms		
No having		
Nil	7	1
Mild (fullness only)	6	3
Moderate	1	3
Severe (incapacitating)	0	7

* Statistical analysis comparing the two means, $t=2\cdot671$, D F $=26$, $0\cdot01 > P > 0\cdot02$

The results are shown in table I Those with normal weight were eating an average of 102% of the calories which they needed theoretically, while those with low weight were eating only 76% This represents a mean deficit of over 600 calories a day in the second group, and is probably enough to account for most of their loss of weight

The daily requirement of protein in health is not known exactly, but it is recommended (British Medical Association 1950) that at least 11% of the total calories should come from this source Those in the group with normal weight were obtaining 10% of their calories from protein Those who were underweight were eating enough protein to provide 12% of their actual calorie intake, but only 9% of the calories they needed There was considerable variation around these means, but it is doubtful whether many patients were greatly deficient in protein

TABLE II—INFLUENCE OF POSTCIBAL SYMPTOMS ON BODY-WEIGHT

—	Severe symptoms (30 patients)	Symptoms absent or mild (45 patients)	χ^2	P (1 D.F)
No with normal weight	4 (*13*%)	19 (*42*%)	7·07	< 0·01
No with low weight	18 (*60*%)	15 (*33*%)	5·21	< 0·05

The severity of postcibal symptoms was much greater in those who were underweight (table I) and accounted for the most part for their reduced consumption of food

The relationship between postcibal symptoms and body-weight was also looked at the other way round—that is, by comparing the number of individuals of normal weight and of low weight (defined as above) in a group of 30 patients with severe postcibal symptoms with the number in a group of 45 who had no symptoms or only mild symptoms The results are shown in table II It is clear that, although severe symptoms were often associated with low weight and mild or absent symptoms with normal weight, the association was far from complete Indeed, a third of those whose postcibal symptoms were minimal were 15 lb or more below their health weight.

Comparative Trial of Methods of Increasing Weight

40 patients who had undergone gastrectomy for peptic ulcer at least two years previously, and who had lost 14 lb or more in weight since, were selected They were on the average 24 lb below their health weight and 25 lb below standard weight *

Preliminary investigations were done in all 5 patients who were anæmic were treated with iron intramuscularly before being included in the trial Correction of the anæmia did not alter their weight The plasma-protein contents were normal in all Chest radiographs showed evidence of healed tuberculosis in 10 patients, in 2 of these the disease had developed after gastrectomy No patient had symptoms of recurrent ulceration Those with severe postcibal symptoms were deliberately excluded from the trial, because they needed treatment by other methods, but 7 had moderate or mild symptoms

Dietary analysis in 12 patients showed a deficit of over 1000 calories a day, which was even bigger than that found in the previous investigation The percentage of calories provided by protein was, however, the same

The patients were allocated at random to one of the following six treatment groups (males only were placed in group 5) (9 patients, after failing to respond in one group, were transferred at random to another)

1 Control (dummy tablets, consisting of flavoured chalk), 8 patients

2 Intramuscular iron (' Imferon ') 5 ml once weekly, 10 patients This was used because it regularly causes increased consumption of food and increase of weight in gastrectomised rats (Welbourn and Doggart 1956, Johnston and Welbourn, unpublished)

3 Intramuscular vitamin B_{12} (100 µg once weekly), 7 patients This was used because its use in the treatment of megaloblastic anæmia following total gastrectomy (Welbourn et al 1956) often causes an increase in weight, and 1 patient who was underweight after partial gastrectomy gained 12 lb in six months while receiving it from her practitioner

4 Dietary supervision by one of us (K A), 10 patients The purpose was to increase the daily calorie and protein intake by (a) the addition of extra protein (meat, eggs, fish, &c) to the three main meals, (b) a daily milk intake of two pints, (c) the addition of a protein supplement (equivalent to 30 g of casein) to one of the pints of milk, and (d) two-hourly high-calorie snacks between the main meals Each patient was seen fortnightly Some needed humouring, while others needed financial help All were given a reasonably free rein where likes and dislikes were concerned

5 Testosterone (sublingual tablets of methyltestosterone, 25 mg daily), 7 patients This was used because of its anabolic effect, debilitated patients rapidly regain weight and strength on this therapy (Reifenstein and Albright 1947) Only male patients were placed in this group because of the possibility of virilisation

6 Iproniazid, 50 mg a day by mouth, 7 patients This was used because of its effect in stimulating appetite (Marks 1957, Scherbel 1957)

All the patients were weighed at the beginning of the investigation and regularly during it The trial was " blind " in that the patients knew that we were trying to help them, but (except for those in group 4 from whom the facts could not be concealed) did not know what treatment they were receiving or that we were particularly interested in their weights

The results are shown diagrammatically in fig 3, which records the total weight changes at the end of eight weeks' treatment No significant change was observed in the control group or in the groups who received iron intramuscularly or vitamin B_{12} Significant gains in weight were found in those who had had dietary supervision, methyltestosterone, or iproniazid The average increase in each group was about 4 lb

Dietary supervision increased the weight in every case, but it was time-consuming and demanded considerable efforts by the patients Moreover, gains that had been achieved with patience were easily and quickly lost if illness or other mischance interrupted the routine

Methyltestosterone was less consistent in its effects 2 patients gained 8 lb in as many weeks, 1 gained nothing, and 1 lost a pound No side-effects were observed. All those who gained weight reported an increased sense of well-being, and 4 of the 7 said that their appetites had increased

Iproniazid was also variable in its effects, but all the patients put on weight, 1 gaining 10 lb and another 8 lb 5 of the 7 patients remarked spontaneously that their appetites had increased and that they were eating more No toxic effects were observed

Continuation of treatment beyond eight weeks caused further slight increases in weight in the methyltestosterone and diet groups (1 patient in the former gained 12 lb in twelve weeks), but not in the iproniazid group Cessation of treatment was often followed by loss of the weight which had been gained

Discussion

The direction of the preoperative change in weight is the most important single factor determining the direction of the postoperative change, and must be taken into account when other factors (such as the type of operation) are being examined The data presented in fig 2 (groups

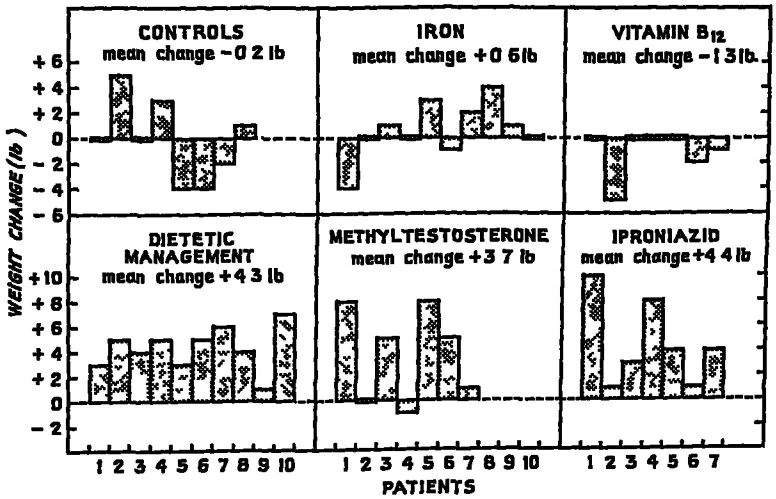

Fig 3—Results of treatment designed to increase body-weight after gastrectomy

Statistical analysis

Controls, iron, and vitamin B_{12}—changes not significant

Dietetic management—t (paired data)=7 9 D F =9 0 001>P

Methyltestosterone—t (paired data)=2 6 D F =6 0 05>P>0 02

Iproniazid—t (paired data)=3 4 D F =6 0 02>P>0 01

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* The standard weight, calculated in relation to sex, height, and age (Kemsley 1952) was taken into account in this investigation because Baron (1954) had pointed out the unreliability of the health weight Although we found, in general, a close correlation between the two (r=+0 84, in 45 observations, 0 01>P>0 001), 5 patients, who were well below their health weights, were excluded because they were in fact at or above their standard weights)

A and B, who account for 99% of the patients) suggest that, whatever the preoperative weight, subtotal gastrectomy tends to make patients assume on the average a final weight 7–15 lb below the health weight The fact that those patients who lose much weight before operation end up 6–8 lb lighter than those who do not, indicates probably that it is harder to regain weight which has been lost than it is to maintain weight at a steady level

An inadequate intake of food clearly accounts for most of the cases of low weight However, in the low-weight group (second investigation) 1 patient was taking 120%, and a 2nd patient 97%, of his theoretical requirements Conversely, in the normal-weight group 3 patients were taking less than 70% The methods of assessing food intake and activity are crude, but the errors are hardly great enough to account for apparent discrepancies of this magnitude Fat and nitrogen balances were not done on these patients, but it is unlikely that losses of these substances in the fæces were great We must for the time being admit that there are a few patients whose low weight we cannot explain

Reduced capacity and postcibal symptoms are clearly important causes of reduced intake, but they are not the only ones It is generally believed that appetite is usually unimpaired by gastrectomy, but the increase in appetite produced by iproniazid and methyltestosterone suggests that anorexia may be commoner than is recognised by either surgeons or patients

Dietary management increases weight by making the best use of the patient's reduced capacity, and iproniazid by increasing his appetite It is not quite clear how methyltestosterone exerts its effect. It is known to promote protein anabolism, but this will not increase weight unless at the same time the intake of food is enhanced, the loss of food derivatives in the fæces is reduced, the metabolic rate is lowered, or excessive fluid is retained in the body 4 of our patients admitted eating more food while taking methyltestosterone, but we have no information on the other possible factors

Although appreciable weight-gains were achieved in several patients, none regained his standard or health weight The best method of increasing weight after gastrectomy remains to be discovered Dietary supervision is difficult, but effective Methyltestosterone is not effective in all patients, and is undesirable because of its possible side-effects We have not yet tried the effects of the so-called "non-virilising" androgens Iproniazid is effective in some, but not in all, and is free from complications in the doses which we have used Possibly other methods will be found, different methods will help different patients, and combinations of remedies will prove more effective than one alone † We do not know how many, if any, underweight patients can be induced to regain their standard or health weights, but our aim should be to help every patient to do so

Summary

A relation was found between the weight changes before and after gastrectomy In general those who lose weight before operation gain weight afterwards, while those who maintain a steady weight before operation lose weight afterwards

Those who are much underweight usually eat too little food

Postcibal symptoms are often associated with low weight

Patients who are underweight after partial gastrectomy gain an average of 4 lb in eight weeks when treated with dietary supervision, methyltestosterone, or iproniazid Dummy tablets, intramuscular iron, and vitamin B_{12} have no effect

Addendum

A further group of 9 underweight male patients was treated with a combination of dietary management and methyltestosterone (50 mg per day)

The mean weight gain at eight weeks in this group was 6 2 lb (S D ± 2 3), which was greater than the gain in any other group (If this group is compared with the "diet" and "methyltestosterone" groups together, t(25 D F)= 2 07—0 05 > P > 0 02)

We are grateful to Sister D I Poole and Sister F M Clarke of the department of surgery, Queen's University, for help with the clinical trial, Mrs P Kemp for secretarial work connected with the trial and for typing the script, Prof H W Rodgers for permission to investigate and treat his patients, Prof C A Wells for his interest and encouragement in the work that was done in his department in Liverpool, Dr E A Cheeseman, reader in medical statistics, and Mr J D Merrett, both of the department of social medicine, Queen's University, Belfast, for their help with fig 1, Miss M Lawlor and Miss E M Wauchob of the dietetic department, Royal Victoria Hospital, for their help, Dr L Goldberg of Benger Laboratories Ltd for supplies of 'Imferon', Dr E W Tapley of Roussel Laboratories Ltd for supplies of methyltestosterone, and Dr J A Marks, of Roche Products Ltd for supplies of iproniazid

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† See Addendum.

PLASMA-TRANSAMINASE ACTIVITY AS AN INDEX OF THE EFFECTIVENESS OF CORTISONE IN CHRONIC HEPATITIS

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ACTIVE chronic hepatitis (Saint et al 1953) is a relapsing inflammatory process believed to be a sequel to overt or subclinical viral hepatitis The liver at necropsy presents the features of so-called postnecrotic cirrhosis In some cases the lupus-erythematosus (L E) cell test and auto-immune complement-fixation (A I C F) test may be positive (Joske and King 1955, Gajdusek 1957) Perpetuation of the hepatitis may depend on an immunological disorder and may be favourably modified by cortisone (Mackay et al 1956) Previous results of the treatment of active chronic hepatitis with cortisone have also suggested that clinical and biochemical improvement takes place (Sborov et al 1955, Last 1957), but the mode of action of cortisone in active chronic hepatitis has remained obscure

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In the absence of other visceral disease the level of glutamic oxaloacetic transaminase in the plasma (PGOT) provides a sensitive index of the degree of liver-cell necrosis (Wróblewski and LaDue 1955)

We present here the results of cortisone therapy in ten patients with chronic liver disease of various types in whom the rate of destruction of the hepatic cells was followed by serial PGOT estimations

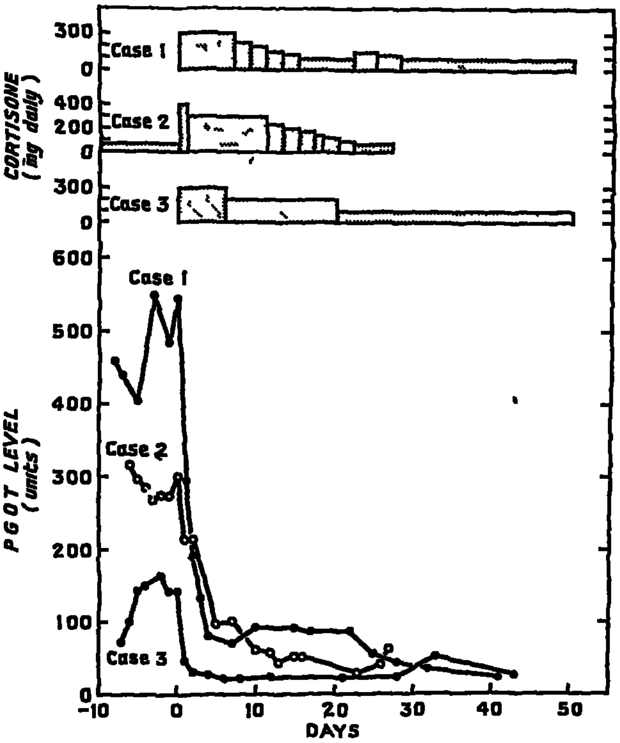

Fig 1—Effect of cortisone in relapses of active chronic hepatitis in cases 1-3 Note pronounced fall of PGOT level coinciding with cortisone therapy

Methods

Serial PGOT activity was estimated by a modification (E N O'Brien and A J Goble unpublished) of the spectrophotometric method of Karmen (Karmen et al 1954) The normal range for this method is 5–28 units The AICF test was made by the method of Gajdusek (1957) Other laboratory methods have been described previously (Saint et al 1953, Mackay et al 1956)

After pre-treatment PGOT activity had been determined for several days, oral treatment with cortisone was begun, usually in the dosage of 300 mg daily, or with the equivalent dosage of prednisolone The dosage was subsequently adjusted to a maintenance dosage of 75–125 mg of cortisone daily

Results

Five patients had active chronic hepatitis In three of these (cases 1–3) with greatly raised PGOT levels there was a precipitate fall in PGOT levels during the first 48 hours of cortisone treatment, followed by a gradual fall to normal levels over the next 2–4 weeks (fig 1)

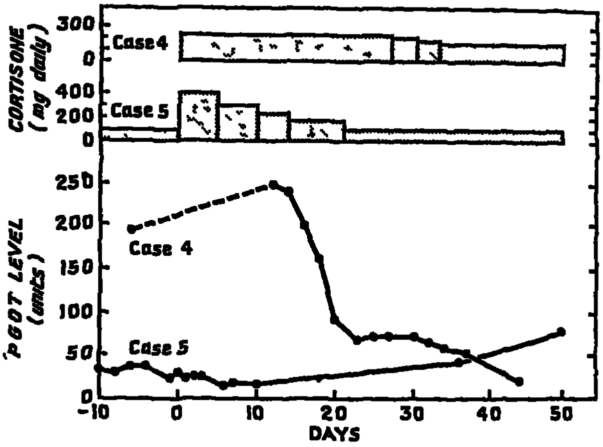

Fig 2—Effect of cortisone in active chronic hepatitis Case 4: note delayed fall of PGOT level (initial data were incomplete) Case 5: note slight fall of PGOT level following increased dosage of cortisone

In case 4 pre-treatment PGOT levels were also greatly raised, but cortisone produced a more gradual fall to normal levels (fig 2) In case 5 the pre-treatment level was only moderately raised, it fell slightly when the cortisone dosage was increased from 100 to 400 mg daily (fig 2)

Of the remaining five cases case 6 had hæmochromatosis with liver failure, case 7 had hepatic necrosis and regeneration in association with a carcinoma of the hepatic duct and portal-vein thrombosis, case 8 had subacute hepatitis of uncertain type, and cases 9 and 10 had chronic nutritional hepatitis In these cases there was no significant fall in PGOT levels with cortisone treatment (figs 3 and 4) However, in cases 8–10 the pre-treatment PGOT levels were not so high

Other pathological and biochemical data are set out in the accompanying table

The addition of 2 5 mg of hydrocortisone succinate to the 3 ml PGOT test system did not influence PGOT activity Cortisone caused no change in PGOT activity in two patients with disseminated lupus erythematosus without liver involvement and in a healthy person

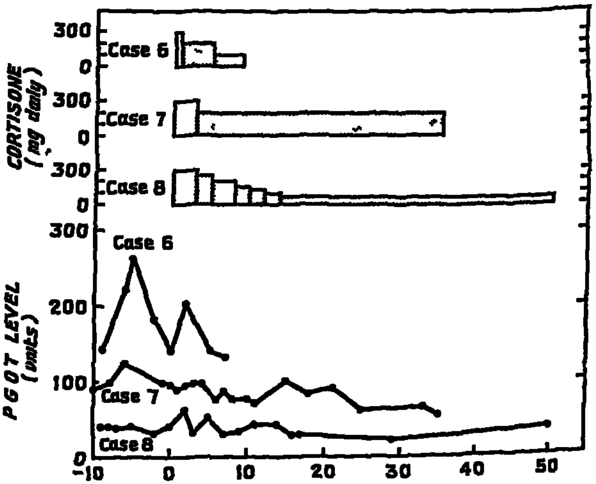

Fig 3—Case 6 (hæmochromatosis and hepatoma), case 7 (cancer of hepatic duct with obstruction), and case 8 (probably ischæmic necrosis of liver) note PGOT levels uninfluenced by cortisone treatment

Case-reports

Case 1.—A housewife, aged 29, was first seen in May, 1956, for diarrhœa which had lasted three months Ulcerative colitis was diagnosed by sigmoidoscopy In October, 1956, she had severe hepatitis, from which she recovered slowly An attack of acute appendicitis in March, 1957, was followed by diffuse suppurative peritonitis requiring drainage In September, 1957, she developed polyarthritis, followed in five days by jaundice

On examination she had many spider nævi, her liver was palpable 2 cm below the costal margin, her spleen was impalpable, and the small joints of her hands were swollen The biochemical results indicated active chronic hepatitis, which was confirmed by liver biopsy immediately before treatment

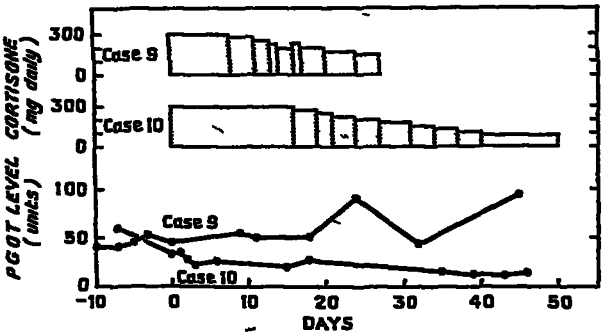

Fig 4—Cases 9 and 10 (nutritional hepatitis) initial P G O T, levels were less highly raised, despite pronounced cell necrosis, no significant change in P G O T levels took place with cortisone treatment.

Cortisone therapy was followed by immediate subjective improvement, a fall in temperature, and a steep fall in the P G O T level (fig 1) The jaundice faded. The patient was discharged well after 4 weeks' treatment, taking cortisone 75 mg daily The improvement in biochemical findings is shown in fig 5 A second liver biopsy, 4 weeks after the start of cortisone therapy, showed decreased necrosis, regenerative activity of the liver-cells, and a slight decrease in inflammatory infiltration.

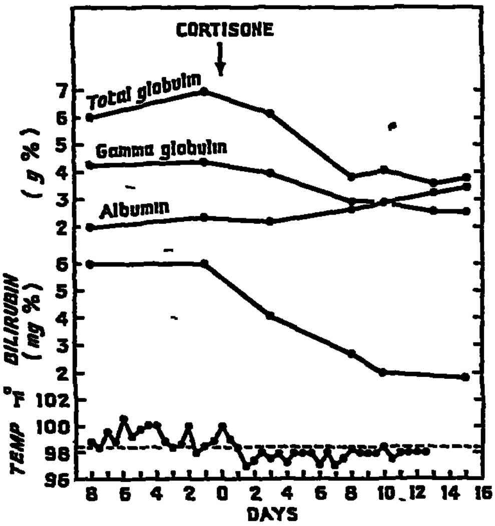

Fig 5—Biochemical findings and temperature chart in case 1 showing improvement during cortisone treatment.

Case 2.—A male clerk, aged 19, had two months' history of malaise, abdominal discomfort, and mild jaundice when seen in December, 1953 Liver-function tests and liver biopsy confirmed the diagnosis of active chronic hepatitis Cortisone therapy produced subjective improvement, although liver-function tests did not alter significantly In October, 1956, splenectomy was done for thrombocytopenic purpura with considerable benefit In October, 1957, the patient presented with two weeks' history of weakness, anorexia, and jaundice, which had begun after he had stopped taking cortisone (75 mg daily) for 3 days

On examination he had moderate jaundice, numerous spider nævi, slight hepatomegaly, and hepatic fœtor Biochemical tests and liver biopsy revealed severe liver damage The

LABORATORY DATA IN 10 CASES OF LIVER DISEASE TREATED WITH CORTISONE

Case no	Diagnosis	Biochemical data*							
		Time† (weeks)	P G O.T (units)	Serum-bilirubin (mg per 100 ml.)	Serum-albumin (g per 100 ml.)	Serum-globulin (g per 100 ml)	Serum-gamma-globulin (g per 100 ml)	Time† (weeks)	Microscopic changes in the liver, (*a*) necropsy (*b*) biopsy
1	Active chronic hepatitis	0	540	6·0	2·4	7·0	4·4	0	Necrosis nodular regeneration, lymphatic infiltration, and slight fibrosis (*b*)
		4	40	1·6	3·6	4·7	2·6	4	Improvement, less necrosis regeneration, and infiltration (*b*)
2	Active chronic hepatitis	0	302	14·0	3·1	5·3	3·7	0	Pronounced necrosis and regeneration, lymphatic infiltration, and fibrosis (*b*)
		3	27	2·4	2·5	4·3	2·8		
3	Active chronic hepatitis	0	140	0·4	3·1	5·9	3·5	0	Nodular regeneration, lymphocytic infiltration, and fibrosis (*b*)
		4	21	0·[illegible]	3·9	3·3	2·0		
4	Active chronic hepatitis	0	194	7·1	2·7	5·3	3·5	0	Some necrosis, active nodular regeneration, lymphocytic infiltration, and fibrosis (*b*)
		4	88	1·3	3·0	3·5	2·7	12	Improvement, less necrosis, regeneration, and infiltration (*b*)
5	Active chronic hepatitis	0	27	0·4	4·1	2·9	1·7	0	Nodular regeneration, lymphocytic infiltration, and fibrosis (*b*)
		2	15	0·4	4·0	3·2	2·0		
6	Hæmochromatosis	0	180	5·7	3·0	4·1		1	Hæmochromatosis, necrotic nodules of hepatoma (*a*)
		1	130	5·2	1·9	3·9			
7	Cholangiocarcinoma	0	97	6·1	2·4	4·0	2·6	1	Extensive cell necrosis nodular regeneration, polymorph and lymphocytic infiltration, fibrosis, and some bile plugging (*b*)
		4	61	9·2	2·3	3·6	2·3	12	Carcinoma of left hepatic duct, infarction and regeneration of right lobe (*a*)
8	?Subacute yellow atrophy ?Ischæmic necrosis	0	40	5·8	2·9	2·6	1·5	0	Some degenerate liver-cells, granulation tissue with many bileducts and lymphocytes (*b*)
		4	19	3·2	2·9	3·3	2·2		
9	Nutritional hepatitis	0	44	1·7	3·1	3·9	0·7	0	Pronounced necrosis and fat-accumulation, lymphocytic infiltration and gross fibrosis (*b*)
		4	40	1·6	2·3	2·8	0·8		
10	Nutritional hepatitis	0	32	0·4	2·6	3·8	1·1	0	Necrosis, fat-accumulation, alcoholic hyaline, lymphocytic infiltration, and fibrosis (*b*)
		4	14	0·4	2·5	4·0	1·2		

* A positive L.E.-cell test was obtained in cases 1, 2, 4, and 5, and a positive A.L.C.F test in cases 2, 3, 5, and 6
† Zero time denotes start of cortisone therapy

patient improved on cortisone 300 mg daily, and P G O T levels fell rapidly (fig 1)

Case 3 —A Hungarian refugee, aged 47, had intermittent epigastric pain, recurrent pain and swelling of the hands and knees, and pale stools and dark urine for several months She had undergone thyroidectomy for thyrotoxicosis in 1949, and cholecystectomy in 1955, when cirrhosis of the liver was observed She had never been jaundiced

On examination she was obese, with numerous spider nævi Her liver was just palpable and tender She had no splenomegaly Biochemical tests and liver biopsy suggested active chronic hepatitis There was 45% bromsulphalein retention She improved with rest in bed but relapsed three months later with lassitude and arthralgia

Cortisone therapy —Within 36 hours of the start of cortisone therapy there was a dramatic fall in the P G O T level from 140 units to a normal value (fig 1), and her general condition improved rapidly

Case 4 —A housewife, aged 57, had six weeks' history of anorexia, nausea and vomiting, pruritus, and deepening jaundice She had been jaundiced 17 years previously

On examination she was jaundiced, and her tender liver was just palpable Biochemical tests suggested severe hepatitis Cholecystography revealed a gallstone Liver biopsy showed active chronic hepatitis Initial P G O T data were incomplete, steroid therapy was associated with an apparently delayed but sustained fall of the P G O T level to normal values (fig 2) Clinical improvement has been maintained

Case 5 —A housewife, aged 40, presented in October, 1954, with active chronic hepatitis and arthralgia (Joske and King 1955, Mackay et al 1956, case 7) She has been maintained in reasonable health on cortisone 100 mg daily since January, 1955

Case 6 —An ordnance worker and storeman, aged 62, had anorexia and tiredness for nine months, diarrhœa for four months, and melæna for one month

On examination he was deeply jaundiced, his skin was grey, he had gross ascites, and the left lobe of his liver was palpable Biochemical tests indicated hepatocellular damage The glucose-tolerance curve was that of diabetes mellitus P G O T levels were considerably raised He was given prednisolone but died in hepatic coma precipitated by massive gastrointestinal hæmorrhage No significant change in P G O T activity was observed (fig 3) Necropsy revealed multiple gastric erosions and hæmochromatosis of the liver with necrotic nodules of hepatoma

Case 7 —A Maltese cleaner, aged 49, had jaundice for two weeks He had undergone two abdominal operations seven years previously for a " tumour ", but had since been well

On examination he had deep jaundice and a few small spider nævi, and 5 cm of liver and 2 cm of spleen were palpable Biochemical tests suggested hepatocellar damage, and liver biopsy showed liver-cell necrosis and nodular regeneration The patient's condition deteriorated over the next three months, and intractable ascites developed

Cortisone produced subjective improvement but no significant alteration in liver-function tests or in transaminase levels (fig 3) This led to a reconsideration of the diagnosis, and laparotomy was done An operative cholangiogram showed obstruction to the left hepatic duct Subsequent necropsy revealed carcinoma of the left hepatic duct, portal-vein thrombosis, hepatic necrosis, and nodular regeneration of the right lobe of the liver

Case 8 —For six weeks a Latvian waitress, aged 57, had had anorexia, malaise, nausea, and pain under her right costal margin, followed by jaundice

On examination she was deeply jaundiced, and her liver was enlarged to 5 cm below the costal margin Ascites and peripheral œdema subsequently developed Biochemical tests suggested hepatitis, but liver biopsy showed mainly granulation tissue and a few surviving liver-cells The diagnosis was thought to be ischæmic necrosis of the liver, but subacute hepatitis was also considered Cortisone produced subjective improvement and a gradual but unsustained fall in the P G O T level (fig 3)

Case 9 —An alcoholic housewife, aged 36, was admitted to hospital in a confused and irrational condition, which progressed to hepatic coma

On examination she was jaundiced and anæmic, with spider nævi and considerable hepatosplenomegaly Liver biopsy showed severe advanced nutritional hepatitis Prednisolone was given without significant effect on transaminase levels (fig 4), although gradual clinical and biochemical improvement took place

Case 10 —An alcoholic male, aged 36, had anorexia and vomiting attacks for nine months

On examination he had exfoliative dermatitis, gross ascites, and an enlarged liver The biochemical tests were in accord with the liver-biopsy diagnosis of chronic nutritional hepatitis He developed liver coma Prednisone and supportive treatment were given, and were followed by slow improvement

Discussion

The glutamic oxaloacetic-transaminase level in plasma and in serum is raised in patients with hepatic-cell necrosis from any cause (Wroblewski and LaDue 1955) The enzyme is liberated from damaged liver-cells, so the P G O T level represents the degree of liver-cell necrosis Therefore, by serial estimations of P G O T in chronic hepatitis, it is possible to follow the rate of hepatic-cell necrosis and to assess the effects of treatment by cortisone

Five of the ten patients studied had active chronic hepatitis In cases 1–3 the P G O T level fell dramatically from previously high values within 48 hours of the start of cortisone treatment (fig 1), this was followed by a more gradual fall to normal values, with steady clinical and biochemical improvement In case 4 the initial fall was more gradual, but the same general pattern was followed (fig 2) In case 5 an equivocal fall of the P G O T level followed a fourfold increase in the dosage of cortisone (fig 2) It may be significant that, at some stage in the disease, the L E -cell test was positive in four, and the A I C F test in three, of these cases On clinical and biopsy evidence, however, they were indistinguishable from active chronic hepatitis of the post-viral type

Five cases with hepatic-cell necrosis from other causes behaved differently (figs 3 and 4) Case 6, with hæmochromatosis, did not respond to cortisone, P G O T levels remaining high, and he died in liver failure Case 7 was initially believed to have active chronic hepatitis but did not respond to cortisone treatment Laparotomy and subsequent necropsy disclosed biliary obstruction due to a hepatic-duct carcinoma, and portal-vein thrombosis with hepatic necrosis and nodular regeneration in the right lobe In case 8 the diagnosis remained uncertain Cases 9 and 10, with nutritional (alcoholic) hepatitis, both had advanced active liver disease and an episode of hepatic coma, yet the P G O T levels were only moderately raised, and were not significantly altered by cortisone therapy

Thus, judged by transaminase levels, cortisone *did not* inhibit liver-cell necrosis associated with hæmochromatosis, biliary obstruction, and ischæmia and alcoholic malnutrition, but rapidly did so in four cases of active chronic hepatitis It is uncertain which cases of active chronic hepatitis will prove to be cortisone-sensitive, there may be a poor response in late cases with well-established cirrhosis

The exact nature of the liver-damaging process in active chronic hepatitis is unknown We believe that the sensitivity of this process to cortisone therapy is more consistent with an immunological concept of hepatocellular injury than with concepts of damage resulting either from continuing viral activity in the liver or from circulatory derangements associated with regenerating nodules An analogy may possibly be drawn with the effect of cortisone in acquired hæmolytic anæmia, wherein cortisone inhibits the damaging effects of an antigen-antibody reaction at cellular level, cortisone may operate in a somewhat similar fashion in these acute relapses of chronic hepatitis

This limited study supports the use of cortisone in acute exacerbations of active chronic hepatitis but sheds no light on the effect of cortisone on the ultimate outcome of the disease It could well be argued, however, that rapid control of the necrotic process might lessen hepatic scarring and disorganisation

Summary

In ten patients with chronic liver disease the rate of liver-cell necrosis was followed by serial estimations of glutamic oxaloacetic-transaminase activity in the plasma before and during cortisone treatment.

In four of five patients with active chronic hepatitis a pronounced fall in transaminase levels coincided with cortisone treatment

In five patients with chronic liver disease of different ætiology there was no significant fall in transaminase with cortisone treatment

This limited study indicates that cortisone reduced the rate of liver-cell necrosis in relapses of active chronic hepatitis, thus favourably influencing the course of the disease

We wish to thank Miss B Paterson for assistance with transaminase estimations, Prof R R H Lovell for generously providing laboratory facilities in the University Department of Medicine at the Royal Melbourne Hospital, Dr L I Taft for histological interpretations, Dr S Weiden for biochemical estimations, and Dr K Fairley, Dr T Hurley, Dr L Rothstadt, and Dr W E King for kindly referring patients

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DIAGNOSTIC VALUE OF SERUM-TRANSAMINASE ACTIVITY IN HEPATIC AND GASTROINTESTINAL DISEASES

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LARGELY as a result of the work of Wróblewski and his colleagues (Karmen et al. 1955, Mason and Wroblewski 1957) determination of serum glutamic-oxaloacetic transaminase (S G O T) activity is widely used as a diagnostic test in acute myocardial infarction and diseases of the liver The liver has been shown to be the main source of serum glutamic-pyruvic transaminase (S G P T), for this enzyme is found in relatively high concentration in the liver In various forms of liver disease S G P T activity is often above normal levels, whereas in myocardial infarction it is not significantly raised unless the liver is also involved (Wroblewski and LaDue 1956, Chinsky et al 1957)

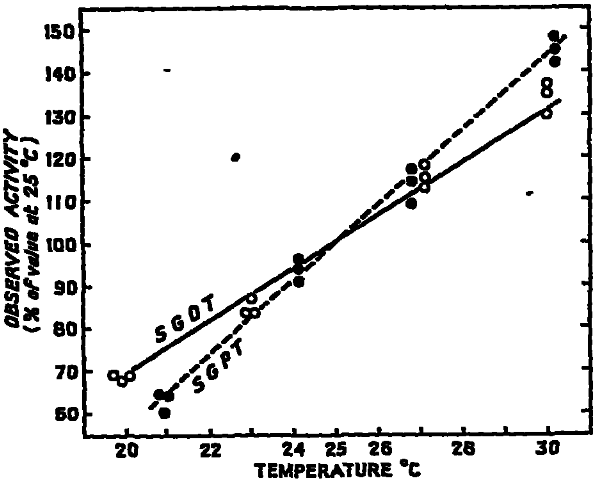

Fig 1—Effect of temperature on S G O T and S G P T activities

The work described here was done to find out if the determination of serum-transaminase activity should be recommended for inclusion in the routine liver-function tests in a hospital laboratory

More than 1000 determinations were done on 226 patients and 50 healthy controls The patients included 66 with ulcerative colitis, of whom 10 had hepatic complications, 13 with obstructive jaundice, 15 with infective hepatitis, 27 with either cirrhosis or chronic hepatitis, 27 with hepatic metastases, 11 with cholecystitis, 35 with miscellaneous diseases of the intestinal tract not involving the liver, and 25 without organic disease

While this paper was being prepared, Madson et al (1958) reported S G O T determinations in various hepatic disorders

Methods

All the results summarised here were obtained by the methods of Karmen et al (1955) for S G O T or that of Wroblewski and LaDue (1956) for S G P T with a 'Unicam S P 500' spectrophotometer In these procedures the transaminase system is coupled with a second enzymic reaction involving the oxidation of the reduced form of diphosphopyridine nucleotide (D P N H)

Temperature—Though the recommended concentrations of reagents and enzymes and the general procedure were satisfactory, we found that fluctuations of temperature caused considerable variations in the results obtained in both series In the original description of the method estimations were made at an unspecified room temperature It was impracticable to apply thermostatic control to the cuvettes in the instrument at our disposal, but our aim was achieved simply by taking the temperature of the contents of the cuvette immediately after the final reading of the optical density The room temperature was varied between 20° C and 30° C, and a series of determinations were made on the same sera Fig 1 shows the effect of temperature on the observed S G O T and S G P T activities Steinberg et al (1956) have described a temperature-correction curve for S G O T with which our results are in close agreement All the results described here were adjusted to 25° C

Blanks—When the sample of serum was clear, we found it possible to dispense with a serum-reagent blank (omitting D P N H), and to use instead a solution of 0·0005*N* K_2Cr O in accordance with the recommendation of Sobel et al (1956) When the dichromate blank was used with a lipæmic serum, however, erroneously high values, due to the separation of particles of serum during the measurement of optical density, were sometimes obtained In these cases a full serum and reagent blank was obligatory Usually this was unnecessary, and a considerable saving of serum, time, and reagents was thus effected

Reproducibility—Numerous replicate experiments showed the reproducibility of the method (including correction of temperature) to be within 10% of the mean, but in the normal and equivocal ranges the variation was within 5% of the mean

Hæmolysis—Since blood hæmolysates may contain up to fifteen times the serum-transaminase activity (Karmen et al 1955) hæmolysis of specimens should be avoided, and serum should be separated without undue delay In our experience minor degrees of hæmolysis did not significantly affect the results These enzymes were surprisingly stable, and the activities of sera did not deteriorate on storage at −18° for several weeks

Colorimetric methods—We also examined the colorimetric methods of Cabaud et al (1956), Wroblewski and Cabaud (1957), and Reitman and Frankel (1957), but we prefer the spectrophotometric procedures because they are less laborious, more reproducible in the equivocal ranges, and require less sera High activities were easily detectable by all four methods

Paper electrophoresis—Serum (80 μl) was applied to Whatman No 3MM filter paper previously ruled into serially numbered 1-cm strips The paper was saturated with barbitone buffer (pH 8 6, μ 0 05) and subjected to electrophoresis by the hanging-strip method at a potential difference of 110 V for fifteen hours While still wet the paper was cut into 1 cm strips, each of which was immersed in 2 ml of 0 067*M* phosphate buffer of pH 7 4 Each strip was found by experiment to contain 0 3 ml of barbitone buffer, thus the total dilution was 2 3 ml in each case SGOT and SGPT activities were determined on 0 5 ml aliquots of each eluate, blank estimations being made on similar strips cut from the same paper beyond the zones containing protein Duplicate electrophoregrams similarly divided into 1 cm strips were run at the same time, these were dried and stained with light-green in the usual way to show the positions of the protein bands

Results

ELECTROPHORETIC MOBILITIES OF SGOT AND SGPT

The electrophoretic mobility of SGOT determined by the method described above was intermediate between that of α_2-globulin and that of β-globulin The results obtained with serum from a typical case of infective hepatitis are shown in fig 2 Similar results were obtained with serum from other hepatitis cases and from patients with obstructive jaundice Owing to the relatively low activity of normal serum it was impossible to apply this method to the serum-transaminases of healthy people, but a comparison was made of the mobilities of SGOT from cases of liver disease and myocardial infarction, they were identical Since our electrophoretic studies were completed our attention has been drawn to a report by Wroblewski (1957) in which a similar conclusion was reached by the moving-boundary method, but no experimental details were given

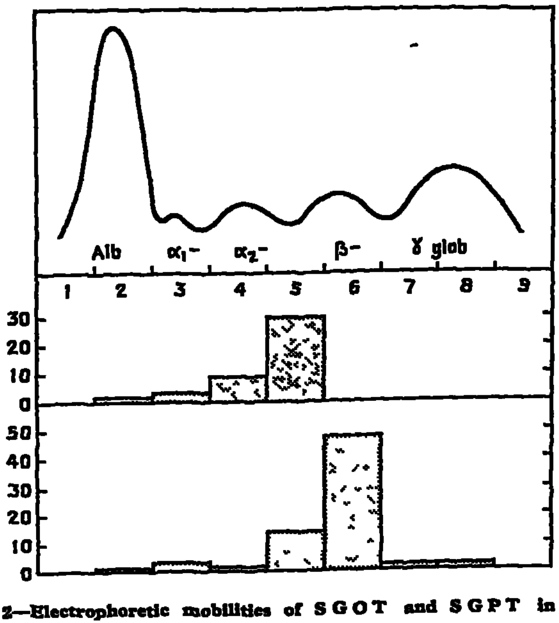

Fig 2—Electrophoretic mobilities of SGOT and SGPT in infective hepatitis

SERUM-TRANSAMINASE ACTIVITIES IN PEOPLE WITHOUT HEPATIC OR CARDIAC DISEASE

Condition	SGOT (units per ml)			SGPT (units per ml)		
	No of persons	Mean ± S D	Range	No of persons	Mean ± S D	Range
Healthy controls	50	19 ± 6	11–38	50	16 ± 5	7–26
Patients without organic disease	25	19 ± 6	8–32	—	—	—
Chronic cholecystitis (non-icteric)	11	15 ± 6	8–27	7	11 ± 5	5–22
Ulcerative colitis without hepatic complications	56	18 ± 7	7–33	22	11 ± 5	5–22
Miscellaneous intestinal diseases not involving the liver*	35	18 ± 7	9–37	20	13 ± 4	4–20

*These included 5 cases of peptic ulcer, 5 of steatorrhœa, 2 of argentaffinoma, 5 of gastric carcinoma, 3 of rectal carcinoma, 5 of carcinoma of the colon, 8 of diverticulitis, and 2 of regional ileitis

SERUM-TRANSAMINASE ACTIVITIES

Normal Values

SGOT and SGPT activities were determined in 50 healthy adults aged 19–50 No significant difference was found between the values given by males and females or by different age-groups The results are summarised in the accompanying table with those obtained in hospital patients with conditions unlikely to affect transaminase levels These figures are somewhat lower than those reported by Wroblewski and his colleagues, who obtained means of 22±7 SGOT units per ml and (at 23° C) 16±9 SGPT units per ml If the latter is adjusted to 25° C it becomes 20±11 units per ml

We suggest that values over 40 SGOT units per ml and 30 SGPT units per ml be regarded as abnormal, provided that the results have been corrected to 25° C

Serum-Transaminase in Liver Disease

A summary of the results obtained is illustrated diagrammatically in fig 3, which shows that, in four main categories of liver disease, transaminase activities may sometimes be of considerable diagnostic importance

Acute hepatitis—Very high levels of SGOT activity (sometimes higher than 2000 units per ml) were observed in acute infective hepatitis, the highest figures being obtained at the onset of jaundice Fig 4 shows the variation in transaminase activity during the course of the disease in 2 cases—one a typical acute infective hepatitis of short duration, and the other a more prolonged and more severe attack The time during which the enzyme activities remained raised varied according to the severity of the disease, from twelve days after the onset of jaundice in one of the cases illustrated in fig 4 to more than thirty-four days in the other The SGOT level was initially higher than the SGPT level in 5 of the 8 cases seen within three days of the development of jaundice, but it fell more rapidly, with the result that, in several cases, the SGPT level was higher at some stage during recovery

1 subicteric case of infective hepatitis showed SGOT 110 units per ml and SGPT 109 units per ml after seven days' malaise

patients with glandular-fever hepatitis with positive l-Bunnell tests were also studied 1 had S G O T units per ml and S G P T 140 units per ml four days r the onset of symptoms, but four days later these els had fallen to 44 and 46 units per ml respectively, 2nd patient's serum, collected soon after the beging of the illness, contained S G O T ·191 units per ml. S G P T 221 units per ml, and four days later these els had risen to 428 and 358 units per ml respectively, the patient had developed jaundice, and the 3rd ient's serum after a week's illness contained S G O T units per ml. and S G P T 242 units per ml A case glandular fever without hepatitis, however, had nor-l transaminase levels

Obstructive jaundice—Of the 13 cases investigated ad obstruction due to carcinoma of the pancreas or of common bileduct and 6 had cholelithiasis All wed raised S G O T levels, mostly 80-200 units per , and in 10 of 12 of these the S G P T activity was also reased, but in only 1 case did it exceed the S G O T lues In contrast with our experience in the hepatitis ses, the transaminase levels remained high until the struction was relieved by surgical intervention, after ich they returned to normal within a week

One of the cases studied showed spontaneous rises and ls of serum-transaminase levels, which, subsequent estigations suggested, were probably caused by the ssage of gallstones

Cirrhosis and chronic hepatitis—These cases were very iable, ranging from well-compensated patients with all fibrotic livers to a patient with hepatic coma The G O T level was raised in 20 and the S G P T in 11 27 cases, the latter exceeding the S G O T in only case

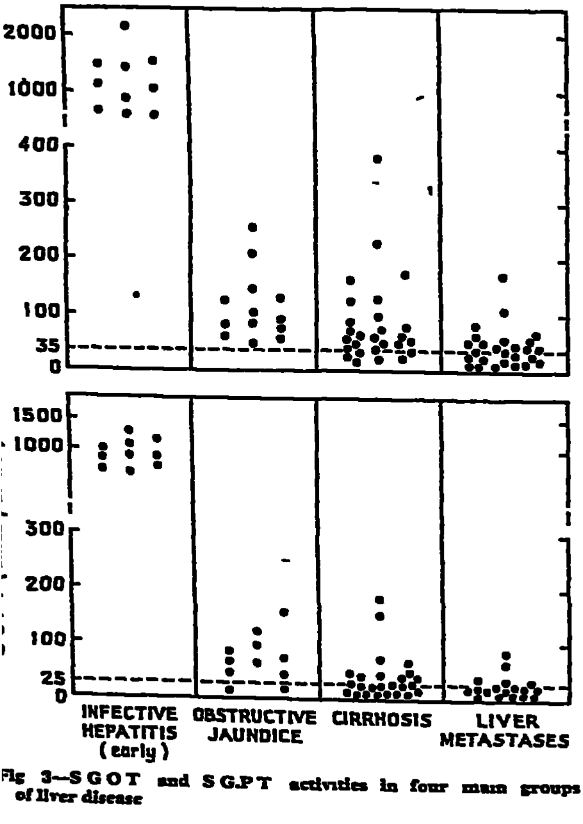

Fig 3—S G O T and S G.P T activities in four main groups of liver disease

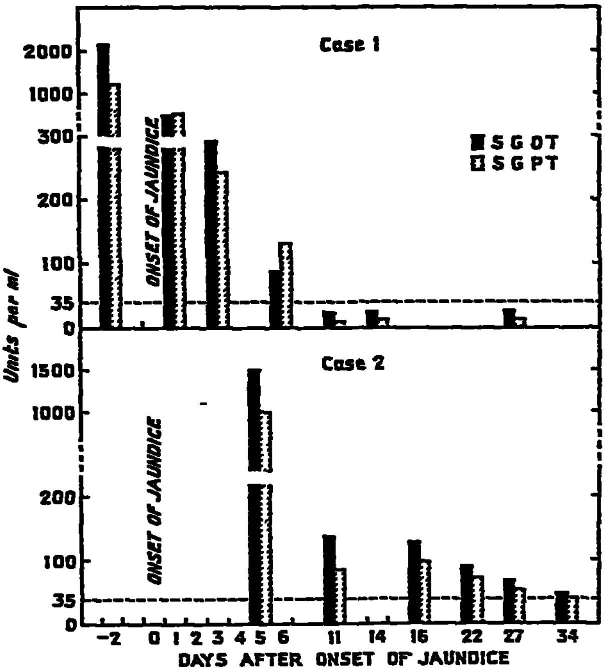

Fig 4—S G O T and S G.P T activities in 2 patients with infective hepatitis.

The raised S G O T values were mostly 40–120 units per ml, whereas the S G P T values only slightly exceeded the normal range The two very high values (fig 3) arose in 2 cases with evidence of acute liver-cell necrosis, one at biopsy and the other at necropsy following death from hepatic coma

Liver metastases—15 of 27 cases showed raised S G O T values and 5 out of 18 raised S G.P T values In each case the raised S G.P T value was associated with a high S G O T value. The highest values (fig 3) were obtained in a case of primary carcinoma of the breast which at necropsy showed massive liver metastases The other S G O T value exceeding 100 units per ml was in a case of prostatic carcinoma in which hepatic secondaries were accompanied by considerable hepatic necrosis In the remaining cases the raised S G O T values were 40–70 units per ml, the S G P T values were usually normal

Ulcerative colitis—The transaminase levels closely paralleled the incidence of concurrent liver disease in this series of patients, for in all the cases in which high values were obtained either clinical or pathological evidence of liver disease was found or other liver-function tests were abnormal In 56 cases without evidence of liver complications the transaminase activities were normal, but in the remaining 10 the S G O T level was raised in 9 and the S G P.T in 3

Both patients with the highest values (120 and 167 S G O T units per ml and 180 and 68 S G P T units per ml) may possibly have chronic hepatitis, but this diagnosis has not yet been confirmed In the remaining cases the S G O T level was only slightly raised (40–60 units per ml)

Toxic hepatitis—3 cases of toxic jaundice were studied 1 of these, which arose as a result of an unsuccessful attempt at suicide by swallowing "safety-match" heads, showed serum-transaminase activities of S G O T 69 units per ml and S G P T 129 units per ml Similar high levels were maintained for fourteen days The 2 other cases were of chlorpromazine jaundice, in which the following figures were obtained initially SGOT 82 and 137 units per ml and SGPT 46 and 204 units per ml We did not have the opportunity of studying the effect of carbon-tetrachloride poisoning in man, but in the serum of rabbits previously treated with this hepatotoxic agent (kindly provided by Dr D Marrack) activities up to 6000 SGOT units per ml and 2000 SGPT units per ml were obtained

Liver infarction—A sample of serum taken from a patient with a liver infarction due to malignant involvement of the right hepatic artery (confirmed at necropsy) gave transaminase activities of SGOT 250 and SGPT 372 units per ml Bilirubin, alkaline phosphatase, and a battery of flocculation tests were all normal

Partial hepatectomy—A case of isolated hepatic secondaries was treated by surgical removal of the involved lobe An immediate postoperative rise to SGOT 800 units per ml and SGPT 800 units per ml was followed by a rapid fall to SGOT 36 and SGPT 57 units per ml by the sixth day after operation As in some of the infective hepatitis cases, the SGPT activity returned to normal at a somewhat slower rate than the SGOT

Discussion

The value of SGOT determinations in myocardial infarction may be regarded as established, for several workers have confirmed the transient rise which takes place during the day or two following the episode (Shabetai et al 1957, Chinsky and Sherry 1957) Wroblewski and LaDue (1956) showed that, in this condition, the SGPT activity was not significantly raised, thus providing a means of distinguishing between the transaminases of liver and heart This finding has been confirmed in this laboratory The SGOT activity was increased in each of 20 cases of myocardial infarction but, although the SGPT level occasionally showed a transient rise and fall, especially in the patients with the more extensive infarcts, it never rose above 40–50 units per ml except in the presence of probable liver damage Further details of these tests are to be published elsewhere

We examined the possibility that these enzymes were different entities by investigating their behaviour on paper electrophoresis We found that SGOT and SGPT have different electrophoretic mobilities and must therefore be different substances, whereas the mobility of the SGOT derived from the heart was identical with that of the enzyme released by the liver It therefore seems probable that liver and heart release the same SGOT According to our experiments the actions of these enzymes were specific, because the SGOT isolated by paper electrophoresis could not utilise alanine as donor molecule Similarly SGPT isolated by the same method had no effect on aspartic acid There is thus no possibility that SGOT and SGPT are one and the same enzyme able to transfer amino groups from various aminoacids

The highest levels of SGOT and SGPT in the serum were found in cases of acute hepatocellular damage, whatever the cause, be it viral infection, chemical poisoning, or physical trauma Activities of SGOT 12,300 units per ml have been reported in carbon-tetrachloride poisoning (Wroblewski et al 1956), a condition we have studied only in rabbits Very high values (over 1000 units per ml) occurred in infective hepatitis at the onset of jaundice, when the SGOT level was usually the higher During later stages the SGOT level was often exceeded by the SGPT level, and in consequence the latter was useful when serum was not available until the fourth or fifth day of jaundice Both tests were valuable in providing an index of severity of the disease The high values were a constant finding in the early stages, whereas in some cases the alkaline-phosphatase and flocculation tests remained normal throughout As an example of the effects of physical trauma may be cited the case treated by partial hepatectomy in which serum-transaminase activities approaching those of the infective-hepatitis range were observed No change was detected in the result of any other liver-function test

Moderately raised levels (80–500 units per ml) were found in various conditions, some of which—e g, glandular-fever hepatitis and chlorpromazine jaundice—were easily differentiated Values of 80–200 units per ml are characteristic of obstructive jaundice and correlated well with the alkaline phosphatase Since such increased activity occurs in obstructive jaundice, probably one of the physiological functions of the liver is to control the circulating levels by excreting these enzymes into the bile in the same way as alkaline phosphatase Both enzymes have been demonstrated in bile from the common bileduct as well as in bile from the gallbladder (Pryse-Davies, unpublished)

Raised values up to SGOT 80 units per ml were difficult to interpret without evidence from other sources They often occurred in cirrhosis and liver metastases, often accompanied by high alkaline-phosphatase activity in the absence of a raised serum-bilirubin level Variations occurred in both these groups, and levels over 100 units per ml were obtained in the presence of hepatic necrosis In well-compensated cases of cirrhosis enzyme activities were either in the normal range or only slightly above SGPT activity was often normal in these two groups, especially in liver metastases, and consequently was not of much diagnostic value in these conditions

The value of SGPT determinations, however, was well illustrated in a patient suspected of myocardial infarction The SGOT values fell from 202 to 146 units per ml over three days, and then, after the patient had experienced a second painful episode, rose to 256 units per ml, thereafter falling to normal values However, these fluctuations were accompanied by similar changes in the SGPT values, suggesting the liver rather than the heart as the source of the SGOT Subsequently, at cholecystectomy, gallstones were found while the common bileduct was patent The peaks in transaminase activities therefore appear to have been due to intermittent biliary obstruction

We conclude that transaminase determinations are useful additions to the range of liver-function tests because a proportion of cases would have gone undetected without their use Except in infective hepatitis and carbon-tetrachloride poisoning, these tests are unreliable in isolation but should be assessed with the results of other tests, especially alkaline phosphatase, serum-bilirubin, and the flocculation tests The use of both SGOT and SGPT is of value in the differentiation of cardiac and hepatic disease, but the absence of increased SGPT activity does not necessarily exclude the liver as the source of raised SGOT levels

Transaminase determinations are of value in prognosis because they enable the severity of active liver damage to be assessed both in hepatitis and in cirrhosis Thus we observed that maintenance of raised values after hepatitis indicated residual complications and delayed recovery We also found that rising levels in cases of liver metastases suggested a poor prognosis, those cases with the highest values showing at necropsy the most extensive infiltration and accompanying necrosis

The occurrence of occasional anomalous results must not be overlooked, however, for raised S G O T and S G P T values sometimes arose as a result of surgical trauma in the region of the liver and the pancreas, after extensive crush injuries involving considerable skeletal muscle damage, and during hæmolytic diseases of various types A very high value found in a case of pulmonary infarction was probably due to prolonged hypotension with consequent liver damage On the other hand, we have not so far found any increase in transaminase activities after the administration of morphine or its derivatives, as reported by Foulk and Fleisher (1957) in patients with biliary-tract disease given codeine phosphate by injection

Summary

The precision and sensitivity of the spectrophotometric method of determining serum glutamic oxaloacetic transaminase (S G O T) and glutamic pyruvic transaminase (S G P T) has been improved by the application of temperature corrections

A study of 50 healthy people and 127 patients in whom no rise in transaminase levels was expected led to the conclusion that values exceeding S G O T 40 and S G P T 30 units per ml should be regarded as abnormal

In an investigation embracing a wide range of liver and gastrointestinal diseases it was confirmed that high values (over 500 units per ml) for both enzymes are characteristic of infective hepatitis and carbon-tetrachloride poisoning

Moderately raised values (100–300 units per ml) occur in obstructive jaundice, glandular-fever hepatitis, and toxic hepatitis (excluding that due to carbon tetrachloride)

Variable results were obtained in cirrhosis and liver metastases, but in 64% the S G O T level was raised above normal values, whereas only about 40% showed increased S G P T activity

Normal values were obtained in gastrointestinal diseases not involving the liver

S G O T showed a moderate and transient rise (up to 300 units per ml) in myocardial infarction, but in this condition the S G P T level usually remained normal

S G P T was thus of considerable value in confirming the hepatic origin of S G O T in certain cases

Used critically in conjunction with other liver-function tests, transaminase determinations were extremely useful

We wish to thank Dr W H Kelleher, Dr J H Watkin, and our clinical colleagues of the Westminster Hospital Teaching Group for sending samples of blood for investigation, and Prof N F Maclagan for helpful criticism The 'Unicam *S P 500*' spectrophotometer used throughout this work was purchased with the aid of a grant to one of us (J H W) from the Central Research Fund of the University of London

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GLUCOSE AND INSULIN IN SCHIZOPHRENIA

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NO-ONE has so far compared the effects of insulin hypoglycæmia and glucose with the effects of glucose alone in the treatment of schizophrenia In a small investigation, therefore, all schizophrenic patients referred to the insulin unit at Powick Hospital in 1957 were divided, by alternate selection, into two roughly similar groups, one of which received insulin hypoglycæmia and glucose, and the other glucose alone

The insulin treatment was given on customary lines, the hypoglycæmia being terminated by intravenous injection of 40–60 ml of 33% glucose followed by sugar by mouth

The fasting glucose patients were brought to the unit at the same time as the insulin ones and were given an injection of sterile water increasing in amount daily up to 3 ml While the insulin patients went into coma, the glucose patients remained in bed, and, in order to occupy them, those capable of it wrote on selected subjects At 10 30 A M during the first week of treatment the glucose patients were given the flavoured sugar drink corresponding to the insulin pre-coma stage The second week they had 20 ml of intravenous glucose each day followed by the drink, the third week 40 ml followed by a drink, and the fourth week 60 ml followed by a drink, from forty to fifty injections in all, comparable to the forty comas of the insulin patients They then had the $1^1/_2$ oz of sugar for their breakfast As much attention was paid to the glucose patients as to the insulin ones, the pulse-rates and respiration-rates being recorded every half-hour, in addition to visits and talks by the medical officer and nurses

The two groups had breakfast together and for the rest of the day were treated as one group for diet, occupational therapy, social activities, &c No sedative was given at night, and after the first week little difficulty in sleeping was experienced by any of the patients Delayed reactions were treated alike in the two groups, and in the glucose group 3 patients experienced " reactions " The average age of the insulin patients was 25 and that of the glucose patients 26 (range 15–42) The length of illness of both groups was from three months to four years

Results

The accompanying table shows the results of treatment

Treatment	Discharged	In hospital	Discharged against medical advice or did not complete course	Total
Insulin	7	6	2	15
Glucose	7	5	3	15

The results were assessed by whether the patients were discharged from hospital or not

During the year, 30 patients who had been diagnosed as schizophrenics by the senior staff of the hospital were treated in the department, 15 in each group Of these, 7 of each group were discharged and remain out of hospital, 6 of the insulin group who completed treatment remain in hospital, 1 discharged herself against medical advice without finishing treatment, and 1 patient was stopped treatment because of poor recoveries Of the patients who completed the glucose treatment 5 remain in hospital, and 3 left hospital against medical advice before completing the treatment

The number of cases is, clearly too small for any satisfactory statistical analysis, and all that can be said is that they show no significant (P>0 05) difference between the two groups This might not hold true for a large series

Whether there is going to be any difference in the relapse-rate between the two groups can be determined only after a considerable time

Summary

Alternate schizophrenics referred for deep insulin treatment were given either deep insulin (15 patients) or glucose only (15 patients)

No significant difference was observed in the discharge-rate of the two groups

I wish to thank Dr A M Spencer, medical superintendent, Powick Hospital, for his help and advice, and for permission to publish this paper, I am also indebted to Mr Tainton and other members of the nursing staff of the insulin unit for their valuable assistance

LUNG ABSCESS AND PNEUMONIA COMPLICATING INFLUENZA

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Last October 41 adults were admitted to the Bromley, Farnborough, and Beckenham group of hospitals with pneumonic complications of influenza These hospitals serve a population of about a quarter of a million, among whom influenza was then epidemic Virus studies were not carried out, and the diagnosis of influenza was made on clinical grounds

13 of the patients had pre-existing chronic chest disease their ages ranged from 47 to 83 (average 63) They presented with the clinical and radiographic picture of a bronchopneumonia, developing from one to four days after the onset of influenza *Staphylococcus aureus* was cultured from the sputum in only 1 Of these patients 6 died, but the other 7 made good recoveries

28 of the patients were previously fit Their ages ranged from 13 to 68 (average 38) Symptoms of pneumonia developed from one to fourteen days after the onset of influenza In 14 patients *Staph aureus* was cultured from the sputum, and in 6 instances it was insensitive to penicillin 15 patients made an uneventful recovery, in 2 there was slow resolution associated with pleural effusion, 3 died of fulminating influenzal pneumonia, and 8 developed lung abscesses

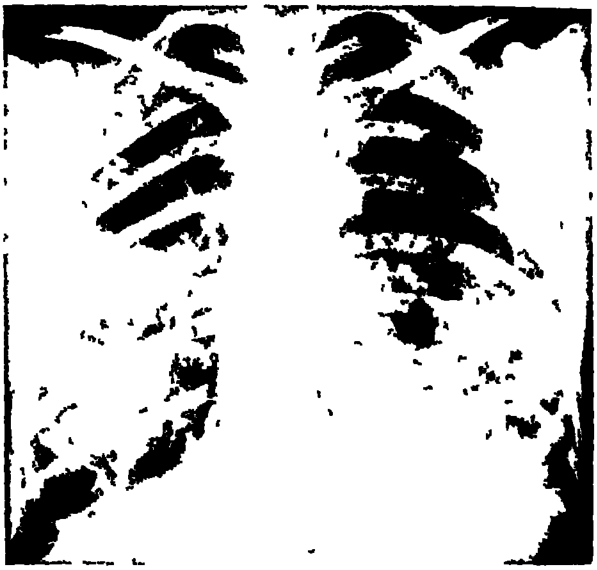

Fig 2—Case 2 Multiple staphylococcal lung abscesses following influenza

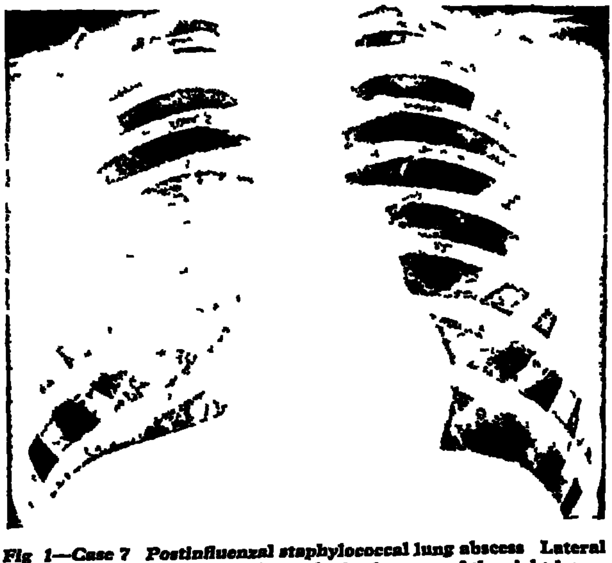

Fig 1—Case 7 Postinfluenzal staphylococcal lung abscess Lateral radiograph showed the lesion to be in the apex of the right lower lobe

As previous reports on last year's influenza epidemic in this country have not recorded lung abscess as a complication, these 8 cases are presented in greater detail

Lung Abscesses

The abscesses varied from a single lesion (fig 1) to multiple cavities throughout both lungs (fig 2) In 1 patient there was an associated empyema (fig 3) The physical signs in the chest were often inconspicuous, the commonest being impairment of percussion note with diminished air entry and râles over the affected areas

6 of the patients were extremely ill on admission, with high fever, tachycardia, dyspnœa, cyanosis, and often delirium Leucocytosis was present on admission in 3

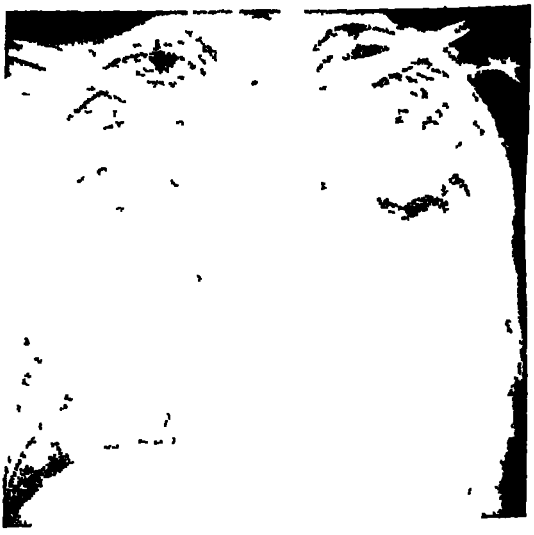

Fig 3—Case 1 Multiple abscesses in both lungs, with left-sided empyema Influenza twelve days previously

es and arose later in 3 more with the development of g abscess The highest total leucocyte-count was ,000 per c.mm.

2 patients were referred because they had failed to over satisfactorily from a postinfluenzal pneumonia ne weeks previously They did not appear gravely ill admission, and neither of them had leucocytosis

Coagulase-positive *Staph aureus* was cultured from the utum in 6 cases, and was resistant to penicillin in 3 In e patient, β-hæmolytic streptococcus was repeatedly und in sputum cultures and in another no pathogens re isolated.

Case 1—A man of 34 developed influenza and stayed in d for two days He returned to work and collapsed, with gh and left pleuritic pain He was admitted ten days later remely ill, with a temperature of 103°F, cyanosis, and delim There was impairment of percussion note with diminned air entry and râles over the whole of the left chest. The est radiograph showed multiple cavities in the left lung with pleural effusion and two cavities in the right upper lobe (fig 3) ucocytes 21,000 per c.mm (polymorphs 80%) Sputum ltures grew β-hæmolytic streptococci on several occasions peated chest aspiration produced purulent fluid which grew e same organism twice The abscesses in both lungs cleared th antibiotic treatment and postural drainage, and the npyema was drained by resection of the 11th rib and insertion a tube Five months later treatment continues for a small npyema cavity

Case 2.—A woman, aged 47, developed left pleuritic pain x days after the onset of influenza. Eight days later she was lmitted seriously ill, with temperature 103°F, pulse-rate 130 er min, and cyanosis with rapid shallow breathing She had een treated at home for three days with penicillin and tetracline. She now had impairment of percussion note and onchial breathing at both bases and bilateral pleural friction ibs Radiography showed consolidation in the middle and wer zones of both lungs with cavities in both lower lobes, the iddle lobe, and the lingula (fig 2) Leucocytes 15,000 (polyorphs 87%) Sputum culture grew *Escherichia coli* on seven ccasions Chest aspiration produced a few millilitres of opaque uid, from which coagulase-positive *Staph aureus* was grown his organism was later recovered from the sputum Treatent with antibiotics and postural drainage was continued ntil discharge from hospital eight weeks later Radiography our months after the onset showed residual scarring in the ngula and a small cystic area in the middle lobe

Case 3—A woman, aged 53, developed influenza from hich she recovered in four days Four days later she became l again with fever, cough, and right pleuritic pain She was dmitted six days later having had oral penicillin for one day espirations shallow and rapid, temperature 104°F, pulse-rate 00 per min There was diminished movement of the right hest with impaired percussion note and low-pitched bronchial reathing over the right upper chest anteriorly Radiography howed consolidation of the right upper lobe with cavitation eucocytes 17,000 per c.mm (polymorphs 74%) Repeated xamination of the sputum failed to produce pathogenic organsms The temperature settled in eight days under treatment with penicillin and streptomycin, and the cavity had closed by wenty-one days, leaving a small area of opacity

Case 4.—A district nurse, aged 49, developed symptoms of nfluenza. Two days later she was too ill to continue work and complained of right pleuritic pain. She was admitted after another two days, delirious and with temperature 103°F, pulserate 105 per min. and respirations 30 There was impairment of percussion note and diminished air entry at the right base, with râles over the whole of the right lung Radiography showed extensive consolidation throughout the right lung Ten days later there had been considerable clearing in the right lower lobe, but a cavity was seen in the right upper lobe The leucocyte-count on admission was 4500 per c.mm (polymorphs 82%), but six days later rose to 11,500 (polymorphs 80%) Sputum cultures grew coagulase-positive *Staph aureus*, insensitive to penicillin and streptomycin but sensitive to chloramphenicol and the tetracyclines Treatment was with chlortetracycline from the day of admission, because she developed a rash after the first injection of penicillin Radiography four months later showed a thin-walled cystic area at the site of the previous abscess

Case 5—A woman, aged 42, developed pleuritic pain and dyspnœa four days after the onset of influenza She was admitted that day extremely ill with cyanosis and dyspnœa, temperature 103°F, pulse-rate 130 per min. There was impairment of percussion note and diminished air entry at the left base Chest radiograph showed diffuse shadowing in the left lower lobe Leucocyte-count was 8000 per c.mm. Subsequent chest radiographs showed a lung abscess in the left lower lobe, and the leucocytes rose to 19,000 per c.mm (polymorphs 78%) Cultures of sputum grew coagulase-positive *Staph aureus*, sensitive to penicillin and other antibiotics She was treated with penicillin and postural drainage, and the cavity had closed by the eighth week

Case 6—A pregnant woman, aged 21, developed a productive cough three days after the onset of an influenza-like illness On admission she was seriously ill, with cyanosis, temperature 104°F, pulse-rate 170 per min, respirations 40 The only abnormal physical signs in the chest were scattered râles in both lung fields, but radiography showed widespread patchy consolidation Sputum cultures grew coagulase-positive *Staph aureus*, insensitive to penicillin Leucocytes 6000 per c.mm She was treated with parenteral streptomycin and penicillin, followed by oxytetracycline when the result of sputum culture was known. There was clinical and radiographic improvement until seven weeks later, when symptoms returned and there was increase in pneumonic consolidation with abscess formation in the apex of the left lower lobe Culture of sputum produced *Staph aureus* sensitive only to erythromycin and chloramphenicol Leucocytes 12,000 per c.mm (polymorphs 85%) Treatment was continued with erythromycin and postural drainage On discharge from hospital, eleven weeks after admission, a chest radiograph showed linear opacities at the site of previous lesions Her pregnancy progressed normally, and she gave birth at term to a healthy infant.

Case 7—A National Serviceman of 19 developed influenza, for which he was in another hospital for several days On return home, he still felt unwell and ran a low-grade fever He was referred to the outpatients department, where chest radiographs showed cavitation in the apex of the right lower lobe (fig 1) He was treated with penicillin intramuscularly for two weeks, followed by tetracycline for ten days Sputum culture showed coagulase-positive *Staph aureus* insensitive to penicillin but sensitive to other antibiotics Leucocyte-count was 8000 per c.mm There was progressive radiographic improvement. Three months later a thin-walled cystic area remained at the site of the previous abscess

Case 8—A woman, aged 27, developed influenza three weeks before admission Two weeks later, she started to have a productive cough and left-sided pleuritic pain She was treated at home with parenteral penicillin and 'Sigmamycin' (tetracycline and oleandomycin), but continued to run a temperature of 100–101°F Radiography at home showed consolidation of the left upper lobe with three lung abscesses On admission, she was not gravely ill but had a cough, purulent sputum, and diminished air entry over the left upper lobe Sputum culture grew coagulase-positive *Staph aureus*, sensitive to all antibiotics Leucocytes 8000 per c.mm. Under treatment with parenteral penicillin and postural drainage, fever abated in three days Three weeks later she was discharged, but subsequent radiographs have shown the persistence of thin-walled cysts in the left upper lobe

Discussion

Postinfluenzal pneumonia caused a higher mortality in patients with long-standing chest disease (6 deaths in 13 cases) than in those who were previously fit (3 deaths in 28 cases) The same high mortality is reported for postinfluenzal pneumonia in patients with cardiac disease (Giles and Shuttleworth 1957) As might be expected, bronchopneumonia developed rapidly after influenza in patients with chronic chest disease and the pathogens isolated showed little uniformity In only 1 patient was *Staph aureus* cultured from the sputum In contrast, it was striking that *Staph aureus* was isolated from 14 of the 28 patients who were previously fit In 6 instances it was resistant to penicillin In 1 of these it was resistant to erythromycin as well, in another to chloramphenicol, and in a 3rd to streptomycin It is probable that *Staph aureus* was present in several of the other patients, though not isolated Sputum cultures may have been affected by the antibiotics, often given before admission In addition, 10 of the patients had an unproductive cough on admission, and, though it became productive in five, they were by that time on full antibiotic treatment

The incidence of staphylococcal infection reported here is in keeping with previous reports on the influenza epidemic (Hers et al 1957, Jevons et al 1957, Roberts 1957) In view of the high incidence of secondary staphylococcal infection, and the statement of Gibson and Belcher (1951) that staphylococcal lung abscess commonly follows influenza, it is perhaps surprising that no such cases are included in previous clinical reports on the pulmonary complications of this epidemic (Morgan and Pickup 1958, Walker et al 1958) Of our 8 cases, *Staph aureus* was cultured from the sputum in 6 and β-hæmolytic streptococcus in 1 These patients all survived and are clinically well In 4 patients, however, thin-walled cysts remain at the sites of the previous lung abscesses in 3 there is residual scarring, and 1 patient still has a small empyema cavity The fact that lung abscess was not fatal in this series may explain its occurrence in only 4 of the 158 fatal cases of influenzal pneumonia reported by Hers et al (1957), Giles and Shuttleworth (1957), and Roberts (1957)

Fulminating influenzal pneumonia occurred in 3 patients, who all died in spite of intensive therapy Cultures taken of the lungs at necropsy gave a pure growth of coagulase-positive *Staph aureus* in 2 cases There was no leucocytosis, and 1 patient had a leucopenia This lack of constitutional response may well be a factor in the fatal outcome In contrast, obvious leucocytosis developed in 6 patients with lung abscess They were admitted in a similarly critical condition, but all survived Lung abscess formed in 3 of these patients while they were in hospital, and leucocytosis was absent until then 5 of the patients with lung abscesses had been under treatment at home for six days or more after developing pulmonary complications The high incidence of lung abscess and the paucity of physical signs suggest the need for radiographic control early in postinfluenzal pneumonia

Summary

41 cases of postinfluenzal pneumonia are reported

In the 13 patients with pre-existing chronic chest disease the mortality was higher (6 died), pneumonia had come on more quickly following influenza, and pathogens isolated by sputum culture showed little uniformity

Among the 28 patients who were previously fit, 3 died from fulminating infection and there was a high incidence of lung abscess (8 cases) *Staphylococcus aureus* was isolated in 14 cases, and was resistant to penicillin in 6 In several others it was probably present though not isolated

Leucocytosis was not seen in fulminating pneumonia but was a feature of lung abscess

We wish to thank Dr N S Plummer, Dr W S L Gilchrist, Dr K O Rawlings, and Dr D N Dobbie, for permission to publish their cases and for their helpful advice and criticism

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Addendum

Since this paper was completed, a combined study group from Dundee has reported lung abscess in 5 out of 262 cases of postinfluenzal pneumonia (*Brit med J* 1958, i, 902) In addition, the Public Health Laboratory Service has reported the necropsy findings in 219 deaths from Asian influenza and found macroscopic abscesses in the lungs in 18% of the cases Lung abscess was hardly ever found apart from staphylococcal infection (*Brit med J* 1958, i, 915)

Medical Societies

SOCIETY FOR THE STUDY OF INFECTIOUS DISEASE

A COMBINED meeting with the Glasgow School of Veterinary Medicine was held in Glasgow on May 3, with Dr T ANDERSON, the president, in the chair

Leptospirosis

Dr IAN McINTYRE dealt with leptospirosis in domestic animals in Britain *Leptospira icterohæmorrhagiæ* produce a serious and often fatal disease in the dog, in pigs the infection is milder and susceptible to antibiotic therapy, and it occurs in calves occasionally *L canicola* infection is widespread in dogs and in pigs A survey of dogs in Glasgow revealed evidence of *L canicola* infection in 35–40%, with a greater prevalence in dogs than in bitches In dogs acute leptospirosis produces a high mortality from uræmia, and recovery is often followed by chronic interstitial nephritis, hypertension, and ultimate renal failure A mild form of the disease can be reproduced experimentally Antibiotic therapy is effective in the pig and the dog if the disease is not too severe

Dr G SANGSTER described a series of 23 cases of canicola fever (18 males and 5 females) admitted to Edinburgh City Hospital The majority were young adults, and familial infection occurred in two instances, at least 12 had apparently been infected from dogs, and 4 from pigs

Bovine Lung-worm

Dr W JARRETT described a method, worked out in the Glasgow School, for vaccination against bovine lung-worm It may be applicable to human helminth infections—for example, trichiniasis and schistosomiasis At first a vaccine prepared from ground-up whole worms was tried, but this reduced the take by only 50% in challenge infections, and the partial immunity set up was sometimes associated with severe eosinophilic pneumonia The method now adopted is to produce an oral vaccine of larvæ devitalised by irradiation with ^{60}Co Such larvæ are unable to progress from the lymphatic glands to the lung On experimental challenge about 99% of the larvæ were killed by the natural defences before reaching the lungs A controlled field trial on 30 calves fed on highly contaminated pastures yielded a fatality-rate of 20% in the vaccinated calves and 83% in the controls Double vaccination with 1000 irradiated larvæ followed by 1000, 2000, or 4000 gave excellent results after very severe challenge tests, and produced extremely high titres of serological antibodies

Toxoplasmosis

Mr R S F CAMPBELL said that toxoplasmosis occurred widely in man, animals generally, and birds Serological surveys in human populations in Britain and the United States have revealed that 20-50% have been infected without any sign of clinical illness In dogs a similar prevalence is found, and lesions occur particularly in the muscles and central nervous system, distemper and active toxoplasmosis often coexist. The only route of transmission definitely known is that from mother to fœtus—possibly as a result of the failure of antibodies to penetrate the fœtal blood-brain barrier In one survey the prevalence of infection was specially high in those working with animals—veterinarians, abattoir workers, rabbit handlers, and rabbit trappers Two tests are used to determine the presence of infection (1) the cytoplasm-modifying test (a dye test producing modified staining reactions), and (2) the complement-fixation test. It has been claimed that the former is not completely specific and that confusion may sometimes arise with other protozoa—e g, *Trichomonas vaginalis* Both tests are, however, used in diagnosis For therapy combined sulphonamide and pyrimethamine is recommended.

Anthrax

Dr R LAMB and Dr W M JAMIESON discussed the hazard of anthrax in those handling bone-meal A third of the bone-meal used in Britain is imported from India, Africa, or South America, and all samples of this examined were positive for *Bacillus anthracis* Yet no instance of pulmonary anthrax has been encountered, and the incidence of cutaneous anthrax is relatively low 13 cases were described—chiefly in farm workers after spraying bone-meal, and in dockers, gardeners, a nurseryman, and a veterinarian after carrying or handling it

Bovine Tuberculosis

Prof J S S INGLIS described the rapid progress in the eradication of bovine tuberculosis since 1935, when the establishment of attested herds by repeated tuberculin-testing was introduced. Within a few years many tuberculosis-free herds were built up In 1950 we passed to the next step, which was to schedule eradication areas in which warning was given that tuberculosis would be eradicated compulsorily from all herds which had not been rendered free within two or three years This has already produced "free" areas covering two-thirds of Scotland, and it is expected that by 1961 the whole of Great Britain will be "free" Nevertheless, in "free" areas about 0 1% of cattle have been reported still to give a positive tuberculin reaction, there are residual pools of infection in human beings, pigs, dogs, and cats, and there are records of infected farm workers infecting clean herds In Glasgow, whereas in 1935 10% of the milk churns proved positive for tubercle bacilli, in 1956 not a single churn was found to be infected and the meat condemned as tuberculous was only a tenth as much as that condemned for the same reason in 1935 In Scotland Certified and tuberculin-tested milk (non-pasteurised) are now the most dangerous grades, because of the risks of brucellosis, salmonellosis, &c.

Staphylococcal Infection

Dr A D T GOVAN, Dr J G P HUTCHISON, Dr MORAG TIMBURY, and Dr T S. WILSON described an outbreak of 14 cases of staphylococcal infection (5 fatal) in a Glasgow maternity unit All were of phage-type 80 In addition 4 cases of type-80 infection (2 fatal) were found among babies recently discharged Nose and throat swabs of the staff revealed a surprisingly low carriage-rate of type 80 (1%), but 3 out of 13 babies swabbed had type 80 in the nose Transmission is believed to have been from baby to baby Closure of the unit appears to be the quickest way to get rid of this infection, in this case it was all over in six weeks The type-80 strain was resistant to penicillin and the tetracyclines, but not to chloramphenicol The low colonisation-rate is difficult to explain. Prof ROBERT CRUICKSHANK suggested that the time available was probably too short for widespread colonisation

Salmonella Infection

Dr HELEN WRIGHT described an outbreak of 3 cases of *Salmonella typhimurium* enteritis traced to a dairy herd in which endemic infection had become septicæmic in some of the cows during calving, with resultant infection of their milk. The probable source was stored straw, which was heavily infested with rats and mice. The risk of salmonella infection of man from bovines is not sufficiently recognised, nor is the bovine septicæmic form in cows during calving Closer liaison between bacteriologists and veterinarians is essential if such outbreaks are to be traced to their source

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New Inventions

A TUNNELLER FOR BYPASS ARTERIAL GRAFTS

THE bypass arterial graft is useful in certain cases of occlusive disease of the major limb arteries One of its main virtues is that exposure of the proximal and distal arterial segments is done through relatively short and separate incisions and the existing collateral circulation remains undisturbed The arterial graft must therefore be drawn through a blind tunnel joining the two incisions Various instruments have been employed to make the tunnel and to draw the graft into position A small œsophagoscope and biopsy forceps are used by Owen and Rob[1] and Crawford and De Bakey[2] suggest a vein stripper

The simple device described here is designed for the purpose and has worked very efficiently The tunneller consists of a streamlined head which serves as a dilator and is so shaped that it will slide easily in either direction The nose of the instrument is perforated by a small transverse hole placed $^1/_4$ in from the tip The head is connected to a flat handle by a rigid but slightly flexible shaft (fig 1) To create a femoropopliteal tunnel, Hunter's canal is opened in the groin and dissection with a finger is begun downwards and medially alongside the femoral artery The tunneller is then introduced into this space and passed distally until the head is felt in the popliteal wound The instrument is then almost withdrawn and repassed once or twice to ensure that the tunnel has been adequately dilated. When the tunneller is felt to run smoothly, its head is exposed in the popliteal space and is withdrawn from the wound. The arterial graft is then secured to it by a suture engaging the graft and passing through the transverse hole in the head (fig 2) When the suture is tied, the artery and the tunneller become locked together, the nose of the instrument fitting snugly into the lumen of the graft. Rotation of the artery in the tunnel is avoided by keeping the flat handle of the tunneller in the same plane as that in which the instrument and the graft are withdrawn to the groin wound It is as well to test that the graft is lying comfortably in the tunnel by irrigating from one end with saline solution and observing a free flow at the other end. The longer tunneller works equally well in an ileopopliteal bypass and is then passed, from above, under the inguinal ligament lateral to the external iliac artery

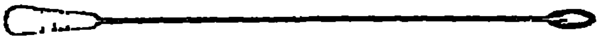

Fig 1

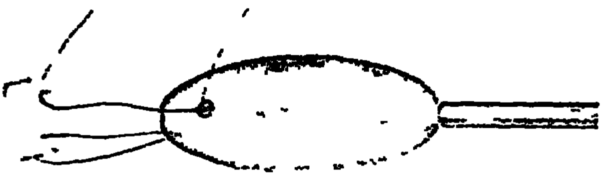

Fig 2

The tunneller is made in two sizes, 19 inches and 16 inches and can be obtained from the Genito-urinary Manufacturing Co Ltd

I wish to thank the Department of Medical Photography, St. Bartholomew's Hospital, for the photographs

St. Bartholomew's Hospital,
London E.C.1

GERARD W. TAYLOR
M.S. Lond, F.R.C.S.

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Reviews of Books

The Essence of Surgery

C STUART WELCH, M S, M D, PH D, professor of surgery, Albany Medical College of Union University, SAMUEL R POWERS, Jr, M D, M SC D, professor of experimental surgery, Albany Medical College Philadelphia and London W B Saunders 1958 Pp 320 49s

GIVEN the time, a well-stocked library, an efficient secretary, and a competent psychiatrist (to dispel lingering inhibitions), any final-year student with a literary bent could write a passable 2000-page “ standard ” textbook of surgery No final-year student could compile a 300-page Essence of Surgery—a task that few experienced surgeons would care (or dare) to tackle It would be too much to claim that Professor Welch and Professor Power have been entirely successful, but their book is a gallant and welcome attempt at the almost impossible Its “ purpose is to present a concept of surgery which will assist readers to a more detailed and definitive study of this division of medicine ” in other words, they aim not at casting a first quick glance, but at exposing the very foundations of their art and science The centre of their discussion is acute physical injury, interpreted in its widest sense, and in broad outlines they consider the therapeutic problems presented by its three main features—loss of body tissue, loss of body fluids, and infection Principles of surgical management are then applied to “ extirpative surgery ” (as exemplified by carcinoma of the colon), to “ reconstructive surgery ” (as practised in skin-grafting), and to “ physiological surgery ” (as in operations on endocrine glands) A chapter deals with the guiding principles of preoperative and postoperative care, and another analyses the basic rules of surgical technique

It is the book’s special merit that it avoids the two most common and most irritating characteristics of Introductions its authors are neither matey nor patronising Indeed, they assume a level of intelligence, a keenness of interest, and readiness to ponder basic issues which few first-year medical students possess and their essay may well prove more helpful to teachers of undergraduates than to undergraduates themselves In the best American tradition the book includes a fine chapter on the history of surgery the authors clearly regard this as part of the Essence and not (as surgical writers often do) as a means of imparting literary *bon-ton* Their hero is Theodor Billroth and he certainly deserves emulation as much as Paré, Hunter, and Lister deserve a rest from hagiographers

Biological Aspects of Cancer

JULIAN HUXLEY, D SC, F R S London George Allen & Unwin 1958 Pp 156 16s

Dr Huxley suggests that autonomous tumours can be logically regarded as members of new biological species with their own specific types of self-replication and with the capacity for further evolution by the incorporation of suitable mutations In judging whether a tumour is autonomous, he adopts the standard criteria of pathology, and he approves the methods and subjects that have in the past been used to study the nature and origin of this phylum Some curious examples of cellular proliferations are, he suggests, well worth more intensive investigation Much space is given to melanomas in drosophila and in old grey horses, though he has doubts, felt by many other workers, about their autonomous status Amphibia are particularly suitable as experimental material

The change underlying autonomy Dr Huxley regards as a deviation of metabolism, and “ any agency capable of pushing cell metabolism in a certain general direction—that of upsetting the normal growth balance so as to favour non-limited replication—is capable of initiating a tumour ” The words used through the decades change somewhat They still leave us ignorant of what this change is

Some more recent topics in cancer research are mentioned, with references to new review articles The opinions of their authors are sometimes adopted without that gruelling critical inspection of the evidence which first-hand experience provokes

Alexander Gordon, M D, of Aberdeen (1752-1799)

IAN A PORTER, M B, lecturer in the department of bacteriology, University of Durham Edinburgh Oliver & Boyd 1958 Pp 92 12s 6d

IN his epoch-making essay on *The Contagiousness of Puerperal Fever*, Oliver Wendell Holmes gave pride of place to the observations of Dr Gordon of Aberdeen, printing in capital letters an extract from his *Treatise on the Epidemic Puerperal Fever in Aberdeen*

> “ But his most terrible evidence is given in these words ‘ I arrived at that certainty in the matter that I could venture to foretell what women would be affected with the disease upon hearing by what midwife they were to be delivered, or by what nurse they were to be attended during their lying-in and almost in every instance my prediction was verified ’ ”

Apart from the essay and the treatise little or nothing has been known of Alexander Gordon, and little credit has been given to him for his shrewd observations Dr Porter’s short biography is therefore important, and he has done it well, finding new material and correcting errors There are some remarkable case-notes the successful delivery of a 16½ lb baby, a cæsarean section, an extra-uterine conception in which the whole skeleton was eventually discharged per rectum over a period of three months, and a curious case of expectoration of bile The best chapter is the one dealing with the epidemic in relation to the state of knowledge of puerperal fever at the time

Alexander Gordon well deserves to stand in the limelight as an important figure in medical history Yet he has been so far forgotten that he is not mentioned in Comrie’s two-volume *History of Scottish Medicine*

Stammering and its Treatment

FRANKLIN BROOK, L C S T, late speech therapist, Huddersfield Child Guidance Clinic London Pitman Medical Publishing Co 1957 Pp 134 21s

MOST doctors know little about stammering, and they are inclined to tell worried parents that the child will “ grow out of it ” if they don’t fuss, and to advise the child, a few years later, not to make such a tragedy of a “ minor ” handicap There is a grain of truth in the doctor’s advice, but without individual understanding and treatment it cannot be guaranteed that the early stammer will fade away, and the later secondary stammer cannot be regarded as a trivial easily surmountable handicap Mr Brook starts by discussing the ætiology of stammer, which he attributes to nervous or emotional instability combined with some illness or stress situation The rest of the book is devoted to a description of primary and secondary stammering and the methods now used for their treatment Relaxation exercises, the use of voluntary stammering, the supportive therapy necessary to help the stammerer persevere, group therapy and “ free speakers’ societies,” and the need for the speech therapist’s guidance, are all discussed

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British Surgical Practice Surgical Progress 1957 (London Butterworth 1957 Pp 442 *52s 6d*)—The new progress volume is even better than usual It makes some slight departures from its accustomed form there are only two original articles (on ulcerative colitis and lesions of the feet in diabetes), and the thirteen critical surveys which follow range more widely than hitherto, reporting the advance in antibiotics, infections, diseases of the alimentary system, pulmonary, vascular, endocrine and orthopædic surgery, gynæcology, breast disease, genitourinary, ear, nose, and throat, and cardiac surgery, and anæsthesia Each survey is followed by abstracts of recent relevant papers, and they are more easily digested thus than in previous volumes, where they were all grouped together The “ noter-up ” (is there not a more attractive name ?) keys the contents of this volume and its six predecessors to the original work The book is a good companion for the busy surgeon who falls asleep over his journals after dinner It is admirably written, beautifully produced, and nicely selective—as one would expect from its editors, Sir Ernest Rock Carling and Sir James Paterson Ross, and their eminent team

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Carcinoma of the Prostate

HUGH YOUNG was forty years ahead of his time when he said that cancer of the prostate was a common disease, he estimated that 1 out of 7 cases of prostatic enlargement in men over 50 was cancerous[1] What was then a bold assertion would now pass as an understatement[2–5] The startling discrepancy between the clinical and post-mortem prevalence of prostatic carcinoma has virtually demolished ideas of cancer as an essentially killing disease FRANKS showed that the "latent" type of prostatic carcinoma is histologically indistinguishable from the ordinary type many latent tumours invade the prostatic capsule, the lymphatics, and surrounding structures[6 7] Yet they neither cause symptoms nor shorten life Cancerous growths in the prostate seem to have a wide range of "biological potential", and this potential we can assess only in retrospect

For the type of cancer which would eventually kill the patient, radical surgery remains the only treatment that offers a prospect of cure[8–10] In any series the proportion of cases found suitable for operation depends on the stage at which the growths are diagnosed and on the criteria of operability FERGUSSON,[11] who has reviewed 313 consecutive personal cases, remarks "In health-conscious communities, where routine examinations are frequently performed, the opportunities for detecting early operable growths by rectal palpation will be correspondingly increased", and this may partly account for the disparity between operability-rates reported from some clinics in the United States and in this country In many patients complaining of mild urinary symptoms the growth will have already become inoperable, and in the overwhelming majority of FERGUSSON's cases there was either extensive local induration or evidence of distant metastases This is a grim state of affairs, and whatever the value of cytological diagnosis, salvation will not come from even routine examination of prostatic smears[12–14] Most surgeons would regard a normal life expectation of less than eight to ten years as a contra-indication to radical surgery[15], and a raised serum-acid-phosphatase level betokens bony metastases[16] On the other hand, neither slight fixation of the growth on rectal palpation nor the discovery of discrete primary nodules, which are occasionally associated with concealed distant deposits, prohibits operation Fixation may be inflammatory rather than neoplastic, and if metastases are revealed postoperatively, they can always be treated by other methods

Only a few years separate the first attempts at radiotherapy from the first radical prostatectomy[5 17], but irradiation still suffers from the severe disadvantage that an adequate dose almost inevitably causes grave damage to surrounding structures Cancer of the prostate was also among the first tumours to be treated by radioactive isotopes[18 19] and FLOCKS[5] has described improved methods of introducing radioactive gold (^{198}Au) But the isotope cannot be confined to the site of injection, and uncontrolled dissemination, even if not necessarily harmful, cannot but cause uneasiness In contrast to radiotherapy, endocrine treatment—dating from the epoch-making work of HUGGINS and his fellow-workers[20 21]—has completely transformed the management of prostatic cancer FERGUSSON prefers oral œstrogens to castration as the first method of growth suppression and he feels that, so long as the dosage is sufficiently high, nothing can be gained from combining the two Stilbœstrol 30 mg daily is tantamount to pharmacological castration, and in FERGUSSON's series the side-effects of 100 mg daily were neither more severe nor more frequent than those from the far smaller doses originally employed[22] Œstrogen therapy eliminates the need for a small but unpalatable operation, it may influence extragonadal as well as testicular sources of androgens, and it may exert a direct cytotoxic effect on the growth itself Newer preparations are on trial, and first impressions with diethyl stilbœstrol diphosphate,[23] given intravenously in doses of 500 mg daily for up to ten days, have been distinctly favourable Breast changes, shrinkage of the genitalia, and occasional nausea and vomiting are common with œstrogen therapy, but they are rarely troublesome enough to require cessation of treatment. Whatever the method of gonadal suppression—and castration still has its advocates[24 25]—three facts can be stated categorically First, œstrogen therapy significantly prolongs life, at any time between six months and three years after diagnosis the mortality-rate of treated patients is roughly half the mortality-rate in earlier untreated series Second, relief from urinary and metastatic symptoms in most cases makes survival more tolerable and the end less distressing Third, most, if not all, tumours show signs of reactivation after months or years In some cases this undoubtedly reflects a change in the tumour cells themselves from being largely hormone-dependent they graduate to a higher degree of autonomy In others, however, reactivation seems to be a response to a compensatory over-production of growth-stimulating hormones in extragonadal sites This second phenomenon forms the rational basis of adrenalectomy[26–28]

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[1] Young H H *J Amer med Ass* 1906, 46, 699
[2] Rich A R *J Urol* 1935, 33, 215
[3] Moore, R. A *ibid* p. 224
[4] Hinman F *J Amer med Ass* 1947, 135 136
[5] Flocks R. H *ibid* 1957 163, 709
[6] Franks, L. M. *J Path Bact* 1954 68 603
[7] Franks L. M *Lancet*, 1956, ii, 1037
[8] Belt, E. *J Urol* 1942, 48 287
[9] Jewett H J *ibid* 1949 61, 277
[10] Millin T Retropubic Urinary Surgery Edinburgh, 1947
[11] Fergusson, J D *Ann R Coll Surg Engl* 1958 22 237
[12] Fergusson J D, Gibson E C. *Proc R Soc Med* 1955 48, 697
[13] Peters H. *Surg Gynec Obstet* 1952, 94 69
[14] *Lancet* 1956 i 489
[15] Scott W W *Practitioner*, 1956, 177, 248
[16] *Lancet*, 1957, i, 674
[17] Deming C. L. *Surg Gynec Obstet* 1922, 34, 99
[18] Hahn, P F Therapeutic Use of Artificial Radioisotopes New York, 1956
[19] Kerr H D Flocks, R. H, Elkins, H B, Culp, D, Evans, T C *Radiology* 1955 64 637
[20] Huggins, C., Hodges, C V *Cancer Res.* 1941, 1, 293
[21] Huggins C., Scott W W Hodges C V *J Urol* 1941, 46, 997
[22] Fergusson J D, Franks L. M *Brit J Surg* 1955 42 422
[23] Hasche-Klunder, R. Willmanns H. *Brit J Urol* 1957, 29 20
[24] Nesbit R. M., Baum W C. *J Amer med Ass* 1950, 143 1317
[25] Staubitz W J Oberkircher, O J Lent M. H *J Urol* 1954, 72, 939
[26] Huggins, C., Bergenstal D M *Cancer Res* 1952, 12 134
[27] Cade S *Ann R Coll Surg Engl* 1954, 15 71
[28] Dao, T L-Y, Huggins C *Arch. Surg* 1955, 71, 645

FERGUSSON submits to operation (which he normally performs in two stages) only those patients who have relapsed after a good initial response to endocrine therapy Hence the 19 patients in his series who were operated on were all men with advanced disease, and most had widely disseminated metastases Adrenalectomy is well tolerated, and, provided the patient adheres to a strict though not too rigorous postoperative regime of cortisone, the risk to life is small Unlike œstrogen therapy, this is essentially symptomatic treatment Striking relief from metastatic bone pain and recession of urinary and pulmonary symptoms can be expected with fair certainty but radiographic signs of metastases usually persist, there is rarely any significant fall in the serum-acid-phosphatase level (though the urinary drain of calcium may be temporarily halted), and it is doubtful if life is materially prolonged

There is a possibility, indeed a likelihood, that growth-stimulating hormones are elaborated in other, unknown, sites even after gonadal suppression and adrenalectomy Various methods of suppressing pituitary function are aimed indirectly at these unidentified target organs, and the procedures now on trial range from formal hypophysectomy to diverse forms of irradiation.[29-33] To say that they should still be regarded as tools of research rather than of therapy is not to deny their value Because neither surgery nor radiotherapy can be relied on to secure total suppression of pituary function,[34] it is fortunate that complete ablation seems unnecessary to produce symptomatic relief " Surgical hypophysectomy," **FERGUSSON** says, " demands a certain standard of fitness which automatically excludes a proportion of otherwise eligible patients, whereas the transnasal introduction of radioactive material into the gland carries little risk " Yttrium, a powerful β-ray emitter, gives promise of a higher success-rate and fewer complications than radon or radioactive gold Two seeds are customarily implanted, one via each nostril, under X-ray control [35], and necrosis ensues over a radius of about 4–8 mm around each seed [36] The chief complication of earlier techniques, but not so far encountered with yttrium, was irradiation damage to the optic chiasma, leading to partial or complete blindness Meningitis is usually prevented by the combined effect of irradiation and of antibiotics, and leakage of cerebrospinal fluid through the sizeable dural perforations necessary for introducing the yttrium seeds usually stops spontaneously The degree of suppression of pituitary function can be assessed indirectly by estimating urinary hormone excretion,[30] [37] by measuring the radioactive-iodine uptake in the thyroid, and by observing the development of clinical signs of hypopituitarism [38]

Leaving the heights of experimental surgery, it is well to remember that simple palliative measures still have a useful place Because of the consistence of the cancerous prostate, urethral dilatation usually yields more lasting benefit than can be expected in benign hypertrophy. If further relief is required **FERGUSSON** prefers perurethral resection (which can be combined with biopsy) to cystostomy drainage, and, where benign hypertrophy coexists, even palliative prostatectomy may be indicated **FLOCKS** [5] aptly remarks that the last fifty years " have made the urologist who works with prostatic cancer a surgeon, a chemist, an endocrinologist, and a radiologist ", but, above all, he still needs to be a man of understanding, patience, and compassion

Water and Tap

To meet the needs of expanding industries and new housing estates, many of the larger *municipalities and* water undertakers have had to augment and improve their waterworks, often far beyond their own boundaries, and in so doing they have often been able to help the villages through which their pipes and aqueducts are laid Meanwhile the Government have been concentrating central financial aid on the smaller local authorities, helping them to bring piped water to villages, hamlets, farms, and whole areas of the countryside where it never ran before A series of Acts of Parliament since 1944 have made £75 million available from central grants, and these have often been supplemented by corresponding amounts from the county councils, so that the rural district council, the county council, and the Government each pay a third of the cost By the end of 1957 some £24 million had been paid or promised as grants from the central funds, and the total value of all new waterworks authorised in England and Wales between August, 1945, and December, 1957, was well over £200 million These figures from the Ministry of Housing and Local Government [39] show that, between the successive waves of economy restrictions, a good deal is being accomplished, and the consequences can be far-reaching The drift from the countryside is not just a matter of the attraction of bright lights, cinemas, and city shops those who have seen a wider world often revolt against inconveniences that their forefathers had to endure The pump or the well in the garden, the path to the little stream, and the old water-butt below the roof may be very picturesque, but to most women a tap in the kitchen beats the lot In these days of a predominantly urban economy, it may seem not unsatisfactory that 95% of the population enjoy piped water But that leaves another couple of million people without it

Like many of our other national institutions, British water undertakings have grown up haphazard—some to meet specific local needs, some to exploit commercial opportunities, and some as part of the traditional patronage of bygone landowners Consequently they present an irrational and uneconomical tangle of pipes and interests But the imperfections go deeper than the

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[29] Luft, R , Olivecrona, H *J Neurosurg* 1953, 10, 301
[30] *Lancet*, 1957, i, 515
[31] Forest, A P M , Peebles Brown, D A , Morris, S R , Illingworth, C F W *ibid* 1956, i, 399
[32] Bauer, K H *Langenbecks Arch* 1956, 248, 438
[33] Pearson, O H , Ray, B S , Harrold, C C , West, C D , Li, M C , Maclean, J P , Lipsett, M B *J Amer med Ass* 1956, 161, 17
[34] Young, S *Lancet* 1957, i, 548
[35] Stevenson, J J *Brit J clin Practice*, 1957, 11, 287
[36] Kelly, W A , Evans, J P , Harper, P V , Humphreys, E M *Surg Gynec Obstet* 1958, 106, 600
[37] Allen, B J , Hayward, J L , Merivale, W H H *Lancet*, 1957, i, 496
[38] Lipsett, M B , Pearson, O H *Med Clin N Amer* May, 1956, p 773

[39] Report of Ministry of Housing and Local Government for 1957 H M Stationery Office 9*s* 6*d*

machinery. Many of the smaller water undertakers are obliged to rely on part-time or semi-skilled staff—which means that too much is left to luck. Whether radical reorganisation would bring more efficiency is a matter of opinion. A national water grid has been suggested, but the countryside seems sceptical about promises of economy and better service from nationalisation of industries, and has said so quite clearly. The Government have compromised by pressing for a limited amalgamation of water undertakings as a first step. At present about half the population are served by the 55 largest undertakers, while the other half are served by about 900 smaller bodies. It is these 900 that are the targets for the Government's fire. They have been encouraged to get together, to prepare plans for amalgamation, they have been exhorted to bestir themselves, and they have been threatened with force. A handful have taken heed, and by the end of last year twelve amalgamation orders had been made, affecting 25 undertakings, and a further eight orders affecting 30 were awaiting the Minister's approval. The Government are steadily intensifying their attack: compulsory powers are to be invoked in five areas, and the shadow lies over many more. It is a pity that such coercion should be necessary and that a rational policy should have to be applied against local opposition. But many a countryman would sooner go down fighting under the might of compulsory powers than be hurried by circulars from Whitehall. It is essentially a matter of public relations. If the Government have neither the time nor the patience to pursue the reasoned approach, then their bulldozer technique seems the only alternative.

But more than administrative efficiency is at stake, for there is a very real need to conserve Britain's water resources and use them to the best advantage. Many underground waterbearing strata are becoming seriously depleted, or contaminated by saline infiltration. Abstraction of well water on a large scale has now been brought under some measure of control, and in water-scarce areas restrictions or refusals have been imposed on sinking extra bore-holes. Also the question of waste during distribution has been raised: some water undertakers tolerate enormous leakage in their systems—sometimes because they find it more profitable to catch additional water for the headworks than to relay the leaking mains. Some authorities eagerly undertake capital expenditure on long loans but cavil at paying for proper routine maintenance out of their current revenue. Water-supplies evoke a curious mixture of business, engineering, and public-service interests, whose interplay can notably affect the happiness and health of a community.

Annotations

ASME

IN theory, the General Medical Council have always wanted each medical school to use its teaching resources in the way it thinks best, but in practice their *Recommendations* have been so detailed as to prevent any considerable departure from the conventional curricula. In education, as elsewhere in medicine, progress is often impossible without experiment, and anyone who doubts whether the present training of medical students is the best possible should be grateful to the Council for the courageous decision they made last year, which promises much more liberty to any medical school which qualifies for it by devising a well-considered plan. In commenting a fortnight ago on Dr Tanner's proposals for a new kind of preclinical curriculum, we expressed some doubt as to whether the teachers of any existing school would be able to agree on so radical a change from what is customary, and we shall in fact be surprised if the majority of schools accept the Council's challenge. But what is important is that a few should do so, and that the way is at last open to pioneers—even if one or two new schools have to be created in order to put their ideas to the test.

Thus the reform of medical education, so often debated in theory, has become something practicable even in Great Britain. No better moment, therefore, could have been chosen for establishing the new Association for the Study of Medical Education (ASME), which should prove as useful in this country as the Association of American Medical Colleges has proved in the United States. The intention is that it shall represent all interests in medical education, but particularly perhaps the people actually responsible for training students, and it will therefore have corporate as well as individual members. These corporate members will be universities, medical schools, and licensing and other bodies interested in medical education, and they will be entitled to send two delegates to each meeting. The functions formally laid down for the Association are (1) to exchange information, (2) to organise meetings, (3) to maintain an information bureau, (4) to encourage, promote, or conduct research into matters connected with medical education, and (5) generally to do such other things as it may think useful. Its first conference will be held on Sept. 25 and 26, when the subject will be Experiment in Education.

Though the Association was formed at a meeting called by the Royal College of Physicians of London, and has the use of the college premises, it is an independent organisation. The executive committee for 1958 has the following members:

Prof. Robert Platt, F.R.C.P. (Manchester), Sir Russell Brain (London), Prof. J. H. F. Brotherston (Edinburgh), Sir David Campbell (Aberdeen), Prof. A. M. Claye, F.R.C.O.G. (Leeds), Dr John Ellis (London), Prof. H. W. Fullerton (Aberdeen), Prof. I. Goldby (London), Prof. J. W. Howie (Glasgow), Dr Alastair Hunter (London), Dr J. G. McCrie (Sheffield), Prof. G. P. Meredith (Leeds), Mr M. F. Nicholls (London), Sir Harry Platt (Manchester), Prof. H. Scarborough (Cardiff), Dr Richard Scott (Edinburgh), and Prof. A. P. Thomson (Birmingham).

ANÆSTHESIA FOR THE EMPHYSEMATOUS

EMPHYSEMATOUS patients give the anæsthetist many problems, some of which have been reviewed by Nunn.[1] Induction of general anæsthesia may be troublesome, since emphysematous patients are usually bronchitic as well, and the sensitive bronchial mucosa is easily irritated by gases such as ether or by the mechanical stimulation incidental to intubation. Moreover, induction may take longer than usual owing to dilution of the gas in the abnormally voluminous lungs, inefficient gas mixing, and reduced absorption of gas from poorly perfused alveoli—

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[1] Nunn, J. F. *Brit. J. Anæsth.* 1958, 30, 134.

although this is not of great practical importance with gases such as halothane and cyclopropane which exert their effect at low blood levels

It is beneficial to abolish hypoxia, but if anæsthesia is conducted during spontaneous breathing and the stimulus to respiration has come to be, not an increased pressure of carbon dioxide, but lowered pressure of oxygen in the arterial blood, then alleviation of hypoxia may lead to diminished tidal volume and dangerous retention of carbon dioxide[2] Artificial ventilation disposes of this hazard but introduces others—including hyperinflation of the lungs, which, by increasing the intrathoracic pressure and preventing venous return, may add cardiac to respiratory embarrassment Considerable pressure may have to be applied in the inspiratory phase to overcome airway resistance, and the sudden reduction of this pressure causes rapid gas flow in early expiration, which may lead to closure of the finer bronchi with gas trapping and hyperinflation Since a grossly subatmospheric pressure applied in the expiratory phase accentuates this tendency, Nunn[1] recommends the employment of only a slight negative pressure (of the order of −5 cm of water) in the latter part of expiration

Rupture of alveoli with escape of gas into the interstitial tissues of the lung and thence to the mediastinum, pleura, and subcutaneous tissues is another possible complication of artificial ventilation,[3 4] especially if high pressures are used, alveoli with free airways will be exposed to the full inflationary pressure, whereas alveoli with obstructed airways will not,[5] so a pressure gradient between adjacent alveoli may become great enough to rupture their walls Sometimes also it is difficult to establish spontaneous respiration after artificial ventilation Auld[6] has reported a case in which spontaneous breathing was not resumed until the patient's arterial-blood-oxygen had fallen to a level low enough to supply the hypoxic stimulus, although in Nunn's[1] experience the chief difficulty has been to adjust the carbon-dioxide pressure to the appropriate level He considers that spontaneous respiration is unlikely to start if the arterial carbon-dioxide pressure is more than 10 mm Hg below the patient's customary pressure, which may not be far short of the level at which respiration is depressed by carbon-dioxide narcosis Hence, as arterial-blood-gas analysis is seldom practicable, it may be necessary to resort to the expedient of alternately raising and lowering the carbon-dioxide pressure until the correct level is found Artificial ventilation is, of course, essential for thoracic operations, and despite its drawbacks it is generally advisable for emphysematous patients undergoing extrathoracic operations as well, since it is the only means of ensuring adequate gas exchange

Preoperative assessment of the patient's respiratory function is important Before thoracic operations the results of lung-function studies will be available to the anæsthetist, but in other cases he will usually have to make his own assessment, often rapidly and with few technical aids The history and physical examination may supply valuable information, but when there is a question of disturbed respiratory function these are not enough The most useful test of ventilatory function is determination of the forced expiratory volume (F E V)—that is, the quantity of air which can be expired in a given time after a full inspiration—and this requires only a spirometer with a simple timing device[7] Figures below normal indicate obstruction to expiratory air-flow, and the findings can be expressed in terms of the more familiar maximum breathing capacity by multiplying by a factor[8 9] The one-second F E V is normally more than 70% of the vital capacity,[10–12] which is estimated at the same time, and a subnormal percentage indicates airway obstruction Successful antispasmodic therapy for asthma will increase the F E V, but it may also increase the vital capacity, so that the F E V percentage may remain unaltered until the vital capacity has been restored to normal[13] failure of a low F E V percentage to rise eventually in response to vigorous therapy despite absolute increases in the F E V and vital capacity is highly suggestive of underlying emphysema Unfortunately there is as yet no simple way of estimating the gas tensions of arterial blood, but, if metabolic alkalosis can be excluded, the serum-bicarbonate content of venous blood will indicate whether or not carbon-dioxide retention is present

In view of the vital importance of preoperative assessment of respiratory function, few will dispute Hugh Jones' opinion[14] that facilities for determining the F E V and the serum-bicarbonate level should nowadays be available to the anæsthetist

CENTRAL HEALTH SERVICES COUNCIL

At the inception of the National Health Service there was a strong hope that the Central Health Services Council, with its well-qualified members, would take a prominent part in the development of the service—offering, as well as responding to requests for, advice on many important issues This hope has been disappointed, and, though some useful surveys and recommendations have been made, successive annual reports by the Council have offered mostly small beer—and, which is inevitable, also rather flat beer, for the findings of the Council or its related committees are often reflected in official policy before the annual report appears The latest[15] covers 1957

The Minister of Health[16] has acted on the recommendations of a subcommittee set up to consider the control of dangerous drugs in hospitals[17] A joint subcommittee of the English and Scottish Standing Medical Advisory Committees, whose interim report appeared in 1956,[18] recommended in its final report last year that the supply of welfare orange juice should be discontinued for children over 2 years of age, and that the vitamin-D content in welfare foods and cereals should be reduced, and these recommendations have been adopted The Standing Dental Advisory Committee considered the report of the Committee on Recruitment to the Dental Profession (the McNair Committee) and informed the Minister that additional clinical teaching facilities were urgently needed

An inquiry by the Standing Tuberculosis Advisory Committee threw further light on tuberculosis in immigrants The committee found that on Sept 11, 1957, 245 temporary residents who had arrived in the previous year were being treated for pulmonary tuberculosis as in-patients, and 205 of these were presumed to have had the disease on arrival in this country, the corresponding figures on May 13, 1953, were 128 and 87 Of these 205 patients 53 were from India or Pakistan, 36 from the Irish Republic, 35 from Hungary, 33 from other countries in Europe, 23 from Commonwealth countries other than India, Pakistan, or the West Indies, 16 from the East (outside the Commonwealth), and 8 from the West Indies, the nationality of 1 was not recorded Apart from the Hungarian refugees, who constituted a special problem, the great majority (120) of the 170 immigrants suspected of having had tuberculosis on arrival were citizens of the Commonwealth or the Irish Republic The Irish medical authorities believed that few of those leaving the country were infectious, there had lately been a vigorous campaign for B C G vaccination, and it was expected that within two years almost all young people emigrating would be tuberculin-positive

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[2] Donald K W *Lancet*, 1949 ii, 1056
[3] Johnston M *Anæsthesia*, 1956, 11, 165
[4] Jaques E *Brit J Anæsth* 1957, 29, 181
[5] Pask, E A *Brit med Bull* 1958, 14, 27
[6] Auld, W *Anæsthesia*, 1956, 11, 263
[7] Gaensler E A *Science*, 1951, 114, 444
[8] Kennedy, M C S *Thorax*, 1953, 8, 73
[9] Cara, M *Poumon*, 1953 9 406
[10] Tiffeneau, R, Bousser, J, Drutel, P *Paris med* 1949, 137, 543
[11] Gaensler, E A *Amer Rev Tuberc* 1951, 64, 256
[12] Pemberton, J, Flanagan, E G *J appl Physiol* 1956, 9, 291
[13] Thomson, W B, Hugh-Jones, P *Brit med J* 1958, i, 1093
[14] Hugh-Jones, P *Brit J Anæsth* 1958, 30, 107
[15] Report of the Central Health Services Council for the Year ended Dec 31, 1957 H M Stationery Office 1958 Pp 24 1s 6d
[16] See *Lancet*, March 1 1958, p 487
[17] See *ibid* Feb 22, 1958, p 422
[18] See *ibid* 1957, i, 1141

The report is presented by Lord Cohen of Birkenhead, who has succeeded Sir Frederick Messer as chairman

UNCOMMON OBJECTS OF THE SEASHORE

BUCKET and spade are now out of date, but it will not be long before the folding boat, the snorkel, and the new bikini are packed into the car and away we go Those who practise by the seaside know that the English summer holiday is medically uninteresting except for drownings (many of which are avoidable) and too many feet cut by broken glass The more dramatic perils of the foreshore are rare in this country A few luckless paddlers stand on weaver fish (and know all about it) [1], but our sharks are too small, our seasnakes are extinct, and it is only rarely—and for reasons which are not very clear—that we are invaded by the highly poisonous jellyfish Last year we had warning [2] of the approach of a fleet of Portuguese men o' war (*Physalia physalis*), but as far as we know no-one was stung Glistening pink and palest blue, these are some of the most lovely things to be seen in tropical seas, but contact is likely to blind the eye to this radiant beauty Even more painful, and sometimes fatal, is the sting of the seanettle, *Cyanea capillata*, which enters home waters even more rarely but has some fame as the origin of one of Sherlock Holmes' more egregious bloomers In the tropics these and other poisonous coelenterates are not uncommon, some of them floating free and some, such as the stinging coral (*Millepora alcicornis*), fixed Most English children are warned against jellyfish and sea-anemones, such old wives' tales must not be treated lightly, but experience shows that many of our native species are seldom or never noxious An authoritative statement on this by a marine biologist would be useful

The structure of the stinging apparatus on the coelenterate tentacle is most elegant Our knowledge of the toxicology of the substance which is injected is based largely on work done many years ago and by modern standards unconvincing, but it seems likely that the most deadly of these creatures produce at least two poisons Local effects range from erythema to necrosis, and the slow healing of wounds caused by coral scratches is probably due to some toxic substance The pain may be local but more often radiates over a wide area and may be sufficient to paralyse the victim The second poison seems to act centrally, interfering with respiration and causing primary shock Drowning is the most usual cause of death, but some of those brought ashore alive die from respiratory failure Morphine (if available) alleviates the pain, but other treatment must depend more on medical art than on the sciences Prevention is limited to the avoidance of jellyfish—especially if they are unlike the familiar kinds—and it is worth remembering that the tentacles are surprisingly long The advice to wear tight-fitting long woollen underwear is unlikely to be acceptable to a generation intent on following Eve as far as the opinion of the public or the Watch Committee will permit

Those who wish to learn more of these perils should turn to an article by Halstead [3] which contains good illustrations of some of the more poisonous coelenterates

THE DOCTOR AS MARRIAGE COUNSELLOR

"AND so they got married and lived happily ever after" From our earliest years we are exposed to propaganda about the effortless bliss attained in marriage Though the experience of our adult years makes clear that there are many exceptions, the ideal stubbornly persists, however much reality diverges from it, and the serenity of the families pictured in the advertisement columns of our newspapers, clustered enthusiastically round a new washing-machine or acclaiming a breakfast cereal, often contrasts harshly with the problems and difficulties of real families described in the news columns

The publicity given to broken marriages today suggests that the institution of marriage is less stable than it was in, say, Victorian days Easier divorce, the social unrest of two wars, the emancipation of women, and Legal Aid have all tended to make the marriage tie less durable But the more durable Victorian marriage often in fact exacted a good deal of endurance, and its durability was sometimes bought at a price of unhappiness that must have been destructive of the relationship between husband, wife, and children If the community accepts divorce more readily today, it also offers marriage support that was unknown in the past The social services offer material help, while the changing climate of opinion and the spread of health education permits a franker discussion of sexual problems The Civil Judicial Statistics published a fortnight ago [4] showed a fall of 578 in the number of matrimonial petitions filed in 1957 compared with 1956, and this decrease is a hopeful sign that the community's growing concern with the breaking as well as the broken marriage may offer stability on less rigorous terms

One of the most useful and youngest of these preventive services is marriage counselling True to our national tradition, it was started by voluntary workers, and much of the work is still in the hands of a group of voluntary societies, including the Marriage Guidance Council which receive a small annual subsidy from the Government In a less formal way, and without even this modest official recognition, the family doctor was, of course, even earlier in the field, and Dr Alfred Torrie has lately suggested [5] that whatever new services the community may offer—through the marriage-guidance societies, the probation officers, or psychiatrists—he should continue with this work To do so, he is favourably placed not only by his knowledge of his patient's family background, but also because the patient can turn to him for help without explicitly admitting that she, or he, has come for a consultation about a marriage rather than a disease In the consulting-room marital problems are seldom presented directly, instead, the patient consults the doctor about some vague ailment, looking back over his own years of practice, Dr Torrie regretted lost opportunities to recognise emotional stress behind a bodily illness The doctor who undertakes this exacting work must, he suggested, avoid rigidity and dogmatism, and practise toleration and patience But his patience must have limits except in a crisis, a patient must not be allowed to take up more than her due meed of the doctor's time "The time allocated has to be presented firmly and kindly just as a dose of sleeping pills with its limited ration " The doctor must be prepared for the patient to express hostility, and must regard it, not as a vote of no confidence, but as a sign that the patient, in search for security, is testing his good will The doctor who is used to laying down regimes for physically ill patients will, Dr Torrie admitted, find it difficult to resist authoritarianism in marriage counselling But authoritarian advice and instructions only perpetuate dependence and immaturity instead the patient must be helped to help herself The doctor must listen but offer no premature advice or solution, he must encourage the patient to find her own answer to her problem and to realise that the decision is wholly her own

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[1] Evans, H M Sting fish and Seafarer London, 1943
[2] See *Lancet*, 1957, ii, 592
[3] Halstead, B W *U S Armed Forces med J* 1957, 8, 1587
[4] Cmd 434 H M Stationery Office 3s
[5] Address to a public meeting held by the London Marriage Guidance Council on May 8

In offering these suggestions Dr Torrie readily admitted that marriage counselling is not a technique but an art, but he believes that it is one to which the general practitioner, with his detailed knowledge of family background, can make a special contribution, as a specialist in first signs and symptoms

SUBLIMATION IN SURGERY

Low-temperature evaporation of water under vacuum to produce freezing, followed by sublimation of the ice, was already well known when Wollaston [1] demonstrated a new method of applying this principle before the Royal Society in 1813 Shackell [2] in 1909 applied the method to the preservation of biological materials, by freezing substances such as serum, virus, meat, and blood in a salt-ice mixture and drying them in vacuo Reichel et al [3] used a rapid method of freezing and drying serum in bulk, and finally raised the temperature again to complete the drying process The result of such a procedure was a porous solid which redissolved with remarkable ease, while many of the properties of proteins were preserved In 1918 Ward [4] foresaw the need for supplies of plasma, but his suggestion was not implemented till 1933 when the first products for clinical use were prepared by freeze-drying [5]

In 1950 Marrangoni and Cecchini [6] used arteries that had been freeze-dried for grafts and reported satisfactory results in dogs The experimental use of dura mater similarly prepared was reported by Sewell and Koth [7] Dura mater obtained aseptically, freeze-dried, and stored in vacuo was used clinically by Campbell et al [8] The introduction of chemical sterilisation [9] by ethylene oxide has led Stern [10] to devise a more practical technique Tissue removed at routine necropsy without aseptic precautions is placed in penicillin-streptomycin solution, trimmed to size and shape, then sterilised in ethylene oxide for half an hour Freezing is accomplished in ten minutes by carbon-dioxide ice and 95% ethyl alcohol, and the material can be stored at −70°C until it is convenient to sublimate the ice at a vacuum of 0 3–0 4 μ over twenty-four hours Grafts are stored in sealed glass tubes at room temperature After reconstitution with water or saline for about twenty minutes, the dura mater is tough and pliable, "a bit more chalky in colour and a bit more leathery or 'chamoislike' but otherwise physically similar to normal dura mater in its surgical properties "

Stern reports the use of the freeze-dried homologous graft in sixteen patients, in whom it proved uniformly satisfactory The tissue was used to repair dural defects resulting from removal of tumours, from previous injury, and after removal of the orbital roof, and no infection attributable to the graft was seen Histological sections of grafted tissue eight days and four months after implantation showed only mild cellular reaction at the suture line, and no more than slight adhesions to the brain From the patient's point of view, it is obviously a great advantage to avoid a second operation site for the purpose of taking a graft of fascia lata Sublimation seems to make homologous grafts if anything more acceptable to the host than are fresh grafts, and rapid freezing to keep the crystals of ice small seems to leave a product that is acceptable in its material properties No doubt further improvements will yet be made Ethylene oxide is volatile, and the vapour is noxious β-propiolactone has been recommended as an alternative [11 12] It must be remembered in grafting a sheet of fibrous tissue that the dead sheet acts mechanically until it is replaced by living fibrous tissue If the area is large this replacement must come from a suitable tissue in contact with one surface of the graft, otherwise growth must take place slowly from the edges, and the centre is likely to break down The new source of grafted dura mater therefore will be suitable enough for laying over a small dural defect, such as a fistula into a nasal sinus This is probably its most important use, the indications for dural repair for other purposes are less certain, and the advantages of a graft over a non-reactive gelatin film are problematical

WORKING PARTY ON HOSPITAL MEDICAL STAFFING

In the House of Commons last Tuesday, Mr Derek Walker-Smith, Minister of Health, announced the names of the members of the Hospital Medical Staffing Working Party They are as follows

Dr R R Bomford, Prof John Bruce, F R C S E, Dr J D S Cameron, Prof Andrew Claye, F R C O G, Sir Kenneth Cowan, F R C P E, Mr H C Edwards, F R C S, Dr G E Godber, Mr Norman Graham, Dr T Rowland Hill, Mr J E Pater, Prof Robert Platt, F R C P, and Mr T Holmes Sellors, F R C S

The working party, which is to study the principles on which the medical staffing structure in the hospital service should be organised, was appointed jointly by the Minister of Health and the Secretary of State for Scotland and the Joint Consultants Committee

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[2] Shackell, L F *Amer J Physiol* 1909 24, 325

[3] Reichel, J, Masucci, P, McAlpine, K L, Boyer, J reported in U S Patent Re-issue, 1939, 20, 969

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Special Articles

THE CHRONIC MENTAL PATIENT
IN INDIA AND IN ENGLAND

W Mayer-Gross
M D Heidelberg, F.R C.P

K W Cross
B Sc , Ph D Birm

J A Harrington
M.A., M D Cantab , D.P H , D.P M , D I.H

Una Sreenivasan
M B , D.P.M

From the All India Institute of Mental Health, Bangalore, and the Departments of Medical Statistics and Experimental Psychiatry, Medical School, University of Birmingham

When one of us (W M-G) visited India for a second time, he was again impressed by the youth of the 500 patients in the Mysore Government Mental Hospital, Bangalore, as compared with patients in most mental hospitals in this country The same impression of youth, of course, is gained in the streets and bazaars of India, where gay young men and women are everywhere to be seen, instead of the prevailing middle-aged people who hastily ply their business in the cities of Great Britain

The Bangalore Hospital, opened in 1937, is the only psychiatric hospital in Mysore State, serving a population of about 2 million In the hope of throwing new light on the universal problem of chronic mental patients, a survey of the chronic patients in this hospital has been made, using the method previously applied in an English urban mental hospital (Cross et al 1957)

The earlier survey was concerned with 1096 patients who had been in hospital for more than two years and comprised 78% of the total number in residence Of these chronic patients, two-thirds of the males and three-quarters of females had been in hospital for ten years or more Only 17% of the male and 9% of the female patients were under 40 years of age and 31% of the male and 50% of the female patients were at least 60 years old The ratio of female to male chronic patients (1 5 for all ages) increased with age In spite of an increasing admission-rate over the last few years fewer patients had become chronic after first admission than in earlier years, but modern treatments had obviously not prevented chronicity altogether, especially among schizophrenics It was also found that retention in hospital not only depended on the presence of offensive behaviour but also was often due to social and other factors not directly related to the biological symptoms of the mental illness Almost a third of the chronic patients had concomitant physical disease, and the proportion for those aged 70 years and over was outstandingly high (59%)

One would naturally expect very different findings in a hospital which serves an Indian community traditionally bound to accept and tolerate the chronic psychotic in its midst. In India, those patients who cannot exist within the family live for the most part as tramps, beggars, or mystics in the precincts of temples or other holy places The psychiatrist has little difficulty in spotting catatonics and paranoids in the entourage of temples and in the streets of towns and villages More than a third of the inmates in a beggars' colony which one of us visited in 1950 were said to be chronic psychotics In our own poor-law institutions in times gone by the state of affairs may well have been the same

Observations

The Role of Age-structure

In the hospital service in India the chronic mental patient constitutes a relatively small problem At Bangalore, at the time of our survey only 132 patients had been in the hospital for two years or more, and the accompanying table shows that over two-thirds of the males and over half the females were under 40 years of age

Life tables for India (United Nations 1954) show that the expectation of life at birth was 32 years, and even at the age of 25 it was only a further 30 years Thus, not only does the Indian chronic mental patient have a much shorter life than his British counterpart, because of communicable and nutritional diseases, but also the low life-expectation in the general population makes the total exposure to risk of mental breakdown far less

Studies in the incidence of mental disorder (Rose and Stub 1956) show age to be an important factor, the highest proportional rates occurring in the highest age-groups The mental disorders of later life are but rarely observed in the Indian mental hospital But, as communicable and other diseases are brought under control in India the expectation of life will rise rapidly and with it the incidence of mental disorder Not only will there be more admissions of mental patients, but also existing patients will live longer and become chronic The increase of pressure on mental-hospital accommodation which has been going on in this country for the past century seems likely to be repeated in India in a much shorter span of time.

Sex Ratio of Chronic Patients

Although the ratio of *all* male to female patients in the Bangalore hospital on any one day was 3 2, there was a small preponderance of female chronic patients The table shows that there were almost twice as many female as male patients aged 40 or over, though the number of such patients was small One explanation of this finding may be differential life-expectation, but available life tables do not indicate that women in India live significantly longer than men The comparatively low expectation of life of Indian women is sometimes attributed to high maternal mortality, and if this is so, chronic female patients may have proportionately less risk of dying from this cause, because mental patients have relatively low marriage and fertility rates

Social and cultural factors are, however, probably more significant In contemporary India, with its predominantly agricultural economy, the joint family system undoubtedly facilitates the return of the mentally handicapped male to his family Whereas the man is able to do simple work on the land cultivated by the family, a woman's value is judged by her childbearing capacity and household skills When a wife's abilities are reduced by mental disorder, there has been, until recently, very little to prevent a husband from discarding her and remarrying Moreover in most Indian cultures parents show greater loyalty to their sons than to their daughters, and this makes it more difficult for a sick daughter to return home Another consideration is the sheltered position of women in Hindu society, which makes a hospital reluctant to discharge a recovered patient if her relatives do not come forward and accept her Male patients are more readily discharged without the assent of relatives

Diagnostic Groups Role of Schizophrenia

The table shows that four categories suffice to classify the male Indian patients as regards diagnosis, and only

DISTRIBUTION OF PATIENTS ACCORDING TO SEX, AGE, AND PRINCIPAL DIAGNOSIS

Diagnosis	Age-group (yr)				
	<30	30–39	40–49	50 or more	Total
Males					
Schizophrenia	16	17	10	4	47 (*78 3%*)
Manic depressive reaction	—	1	—	2	3 (*5 0%*)
Epilepsy with postictal confusion	5	2	—	—	7 (*11 7%*)
Mental deficiency	—	1	—	2	3 (*5 0%*)
Total	21 (*35 0%*)	21 (*35 0%*)	10 (*16 7%*)	8 (*13 3%*)	60
Females					
Schizophrenia	7	18	12	11	48 (*66 7%*)
Manic depressive reaction	1	3	3	1	8 (*11 1%*)
Epilepsy with postictal confusion	1	4	2	—	7 (*9 7%*)
Mental deficiency	2	—	2	1	5 (*6 9%*)
Other	1	1	1	1	4 (*5 6%*)
Total	12 (*16 7%*)	26 (*36 2%*)	20 (*27 7%*)	14 (*19 4%*)	72

four females had principal diagnoses other than these Schizophrenia accounts for slightly more than three-quarters of the male patients and two-thirds of the females Though one should be cautious in comparing diagnostic groups of Indian and English patients, schizophrenics occur in roughly the same proportions of the two series Such a finding may not be true of other hospitals, but it would certainly not go against the expectation of many experienced psychiatrists who have worked in both countries The relatively high proportion of epileptic psychoses is of interest, but the numbers are too small for conclusions

The vastly different social and cultural backgrounds from which the two groups are drawn suggests that these factors are not of major importance in causation or in preventing chronicity If early childhood experiences and other environmental factors are crucial in schizophrenia it seems remarkable that certain schizophrenics tend to become chronic mental patients in spite of different ethnic backgrounds, though the findings in some small closed communities would not support this view (Eaton and Weil 1956) The studies of Slater and Shields (1953) indicate the major importance of genetic endowment in predisposing to schizophrenia, but whether or not a given person develops schizophrenic illness may well be determined by environment

Discharge of Chronic Patient

Underemployment and other social and economic circumstances prevailing in India make it easier for the family to devote time and attention to the welfare of a handicapped member Though poverty and overcrowded living conditions are widespread, these factors do not seem to play as great a part as social attitudes and customs

Many chronic patients who are not visited in hospital by their relatives belong to families which have broken from the obligations of the joint family system, lack strong family ties, and have no dominant elders who think it their duty to tend sick members at home When the elders dominated the family they often sacrificed the welfare of other healthy members to keep a psychotic relative out of hospital and to maintain secrecy about the illness Once such a patient is admitted, discharge may be made difficult by the fear that his return will ruin the marriage chances of the young women in the family It is hard to foresee what would happen to the still existing family sense of responsibility for its mentally sick members if full social insurance and the Welfare State were introduced into India

The public concept of mental disorder remains somewhat primitive in India In the countryside the patient is nearly always treated for "possession" If rituals and rites fail, he is regarded as having "brain disorder", which is believed to be incurable Once such a patient is admitted to hospital, the family are very sceptical of possible recovery and reluctant to receive him back, even if there has been a good response to treatment But, considering how far away they live, and how difficult the journeys, a surprising number of relatives visit and willingly accept the patient home albeit sometimes to physical restraint in the cowshed if he relapses

Reflections

These observations have some bearing on the problem, in this country as in India, of caring for mental patients within the community, as now so often advocated While few would dispute the general desirability of family care for the mentally handicapped, the current social pattern in Britain is very much against accommodating abnormal people in the community Only well-preserved patients are acceptable Behaviour which in India would go unheeded would in this country soon be brought to the notice of the police and the duly authorised officer, with the almost certain consequence of admission to hospital Though many psychotics who do not show dangerous propensities can live harmlessly outside hospital, they can do so only if the community is prepared to be tolerant and make allowances for them Moreover, for success, community care requires an adequate and active aftercare service under psychiatric direction

With life-expectation still increasing in Britain, a continuing change in the age-structure of mental patients is inevitable Mental disorders in general will almost certainly become more prevalent, and there is likely to be an increase in non-organic psychoses, which, since they are not killing diseases, are liable to become chronic People with a tendency to develop schizophrenia or manic-depressive psychoses late in life, after the normal period of childbearing, will not be weeded out by natural selection

Our earlier survey (Cross et al 1957) showed the importance of the double handicap of mental and physical disorder in the same patient, and the frequency of this combination increases rapidly with age Even when neither mental nor physical condition is severe in itself, they may together require hospital care for long periods

The solution of this difficult problem cannot be found by pulling down chronic wards (Bickford 1955) or by adding small psychiatric units to general hospitals Existing chronic wards should be improved, and planning of psychiatric hospital accommodation should not merely be directed to the treatment of recent and acute cases Though better domiciliary care is needed, it is unlikely to solve more than a small part of our problem Recent experiments in this field have led to an unjustified degree of optimism (*Lancet* 1958) In spite of modern methods of treatment and some increased tolerance for the abnormals in the population in the West, all indications are that the demand for chronic beds will grow rather than diminish throughout the world Some of this need can, of course, be offset by providing hostels and other halfway-house accommodation, though those advocating such facilities should not blind themselves to the fact that a hostel can be just as much a chronic ward with a new name and less medical and nursing care Advances in mental health are not made by administrative dodges or by giving new names to old problems

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GENERAL MEDICAL COUNCIL

SESSION JUNE 3–5

SIR DAVID CAMPBELL's presidential address at the opening of the Council's 196th session was summarised last week (p 1220)

BRITISH PHARMACOPŒIA

Dr H GUY DAIN, re-elected chairman of the Pharmacopœia Committee, reported that Prof E J Wayne had been appointed chairman of the Pharmacopœia Commission The committee had considered the problem, which had to be solved before the next *British Pharmacopœia* was published, of legal difficulties in the transfer from the Imperial to the metric system

DIPLOMA IN PUBLIC HEALTH

The Council received the annual returns of examinations for diplomas in public health in 1957 These showed that no examinations were held by ten universities, including Oxford and Cambridge, and the Scottish and Irish Conjoint Boards 202 persons passed the examinations, and 40 were rejected The largest number of candidates (60) presented themselves at London University, and the next largest (19) at Edinburgh

UNIVERSITY COLLEGE OF THE WEST INDIES

Dr E R BOLAND, moving the recognition of the University College of the West Indies for the further period 1959–61, said that great strides had been made by this University College, which had already reached quite a high standard Certain further facilities had been recommended by the University of London The provision of the money necessary for these developments had been rather held up by the formation of the Federation of the West Indies, but the university had been assured by competent authorities that the money would be forthcoming The recommendation was agreed to

Medical Disciplinary Committee

THE PRESIDENT announced that the committee were now in a position to sign the revised rules of procedure If the Privy Council approved these, they would be laid before Parliament, and unless any objection was raised they would come into operation They included a new evidence rule devised in accordance with advice given by the Judicial Committee of the Privy Council

The committee also approved a new statement to be substituted for the Warning Notice hitherto published at the front of the Medical Register As now listed, the grounds on which practitioners have been adjudged guilty of infamous conduct in a professional respect include "gross and/or prolonged neglect of duties, and disregard of personal responsibilities to patients" and "improperly obtaining or attempting to obtain payments from the National Health Service or otherwise to which they were not entitled"

RESTORATIONS AND ERASURES

The Registrar was directed to restore to the Register the names of *Ernest Benjamin Dawe* and *Patrick Laurence Lyons* *William Arthur Channugam Nason* and *George William Franklin* were unsuccessful in their applications for restoration

Arthur George Davies, registered as of 2, Four Elms Road, Cardiff, Glamorgan, M R C S (1940), was summoned on a charge of infamous conduct in a professional respect in that he committed adultery with a woman patient, of which he was found guilty by the Divorce Court He was not present and was not represented Mr G J K Widgery, solicitor to the Council, said that at the Divorce Court Dr Davies had been ordered to pay the husband £1000 damages, this had not been paid, a receiving order had been made against him, and he had now been adjudicated a bankrupt. The committee directed the Registrar to erase his name This is subject to an appeal being entered within 28 days

Robert Lindsay, registered as of 8, St Ninian Drive, Inverness, M B Glasg (1945), was charged with being convicted at Inverness of stealing a newspaper from a railway bookstall, and committing a breach of the peace He was not present and was not represented

Mr Widgery said that Dr Lindsay was drunk and creating a disturbance, challenging people to fight, he was also seen to take a newspaper from a bookstall He had appeared before the committee in May, 1955, as a result of four convictions between November, 1951, and March, 1955, for committing breaches of the peace in Inverness where he lived Judgment had been postponed for two years, and last May the case had been dismissed ' I understand he had not been practising as a doctor since 1955, but is employed by a firm of public works contractors in the North of Scotland," concluded Mr Widgery

By reason of the conviction, the committee directed the erasure of Dr Lindsav's name He can enter an appeal to the Privy Council

POSTPONED JUDGMENTS

The committee received satisfactory information concerning *David Philip Lewis-Badgett* and *Joseph John McMenemy*, for whom judgment had been postponed This concluded their cases

Last November the committee postponed judgment for six months in the case of *Hari Shankar Badve*, provisionally registered as of Central Talkies, Malegaon (Nasik), Bombay, India, M B Bombay (1953), who had been charged with submitting false certificates of experience for full registration While the committee now judged him guilty of infamous conduct in a professional respect, after considering testimony to his conduct, they did not direct the Registrar to erase his name from the Register

In May, 1956, judgment was postponed for two years in the case of *James Watson Richmond*, registered as of Rossleen, Kelty, Fife, M B Glasg (1929) Dr Richmond did not appear and was not represented. After consideration in camera, the President announced that judgment was postponed until next November

Presenting the case of *William Frank Cruickshank*, registered as of c o Milne, Broxy Cottage, Westmuir, Cruickshank, Angus, M B Glasg (1935), Mr Widgery, said that from May, 1954, the committee had three times postponed judgment The Chairman said to Dr Cruickshank

> "The Committee once again are not satisfied that the evidence concerning your habits and conduct would warrant them in discharging the case They are, however, prepared to give you one further opportunity—and may I emphasise 'one more opportunity'? —of satisfying them as to your habits and conduct They have therefore postponed judgment for a further period of six months"

Patrick Francis MacDonald, registered as of c/o A MacDonald, solicitor, Main Street, Granard, Co Longford, M B N U I (1941), had had judgment postponed for one year following convictions in 1950, 1952, and 1956 involving drink Mr Taylor, appearing in his private capacity for Mr MacDonald, said that he had again been convicted Judgment was postponed for a further year

Arthur Alfred Hill, registered as of 25, Holywood Road, Belfast, M B Belf (1926), had been convicted in 1950 of driving a motor-car when under the influence of drink and in 1957 of supplying tablets to another person with intent to procure a miscarriage (for which he was sentenced to three months' imprisonment) At the previous session the committee had deferred this case so that the Council's solicitor might obtain further information on the circumstances of the second conviction

Mr Widgery then said he had had great difficulty in obtaining any information He now told the committee that he had been unable to get any documents from Belfast except by subpœnaing a detective sergeant This detective sergeant produced statements made to the police Mr Widgery said that Dr Hill supplied some ergot tablets to a man whom he would call "Mr C" which Dr Hill knew were to terminate the pregnancy of a woman These tablets did not have the desired effect The girl did not have a miscarriage and gave birth to a baby In his evidence the detective sergeant said that a man was accused as well, he was found not guilty Dr Hill "Is it a fact that the woman concerned had not taken any tablets?" Witness "That is so" He agreed that he took a statement from the doctor at 10 o'clock at night, when the doctor, who had been ill, got out of bed to make it

The committee took a very grave view of the convictions They were prepared nevertheless to take into consideration the representations Dr Hill had made and the testimonials he had submitted, and postponed judgment for one year

John Holbrook Hill, registered as of Locks Park, Brixham, Devon, M R C S (1938), was charged with having been convicted at Brixham in 1955 of being in charge of a motor-car when under the influence of drink and at Exeter Assizes last November for driving a motor-car when under the influence of drink and causing the deaths of two persons by dangerous driving, when he was sentenced to six months' imprisonment for each offence, to run concurrently

Mr J Talbot, counsel, said that on neither occasion was Dr Hill engaged on any medical duties He now almost abstained from alcohol Mr Talbot read testimonials which, he said, showed that his client was not only a man wedded to his work but also a man of ability and some considerable value to the community where he practised

The committee postponed judgment for two years

John McGregor, registered as of Blythswood, Carronshore, Falkirk, Stirlingshire, M B Glasg (1940), had two convictions of driving a motor-car when under the influence of drink—the first in 1953 and the second in 1958 The Chairman told him that these convictions indicated habits which were not only discreditable but might be a danger to patients Judgment was postponed for a year

Mr Bayliss appeared as solicitor to the Medical and Dental Defence Union of Scotland in the case of *James Stewart MacDonald*, registered as of Knockdale, Beith, Ayrshire, M B Glasg (1925), who had been convicted in 1949 and 1957 for driving a motor-car when under the influence of drink or drugs Mr Widgery said that he had also been before the General Medical Council in 1943 following convictions in 1937 and 1942 In the light of his earlier record the committee regarded with grave concern the convictions now proved, but postponed judgment for a year

NAVAL COURT-MARTIAL NOT A "COURT"?

Fintan Anthony Lennan, registered as of Little Manor, Frittenden Green, Staplehurst, Kent, was charged with having been convicted at a Naval court-martial on two charges of gross indecency Mr N Leigh Taylor, solicitor, argued that this was not a conviction within the Medical Act, 1956, which said that "if any fully registered person (a) is convicted by any court in the United Kingdom or the Republic of Ireland of any felony, misdemeanour, crime or offence" the committee might direct his name to be erased from the Register Mr Taylor submitted that the words "by any court" must mean a court of competent criminal jurisdiction If courts martial were included, why not the benchers of Inns of Court, the Solicitors' disciplinary committee, the medical services committees, or the stewards of the Jockey Club? If a court martial was included, the committee would have to accept as offences everything which could be tried by a court-martial—e g, being improperly dressed on parade Further, a conviction by a Naval court-martial was not a conviction for any other purpose of law His client, if anyone chose, could be brought before a competent criminal court and only then would he be convicted The inclusion of courts-martial led to the absurdity that if the same officers had "convicted" his client in Malta, on the same evidence and with the same judge advocate, the "conviction" would not be within the Medical Act, whereas at Plymouth it was

Mr C P Harvey, Q C, the legal assessor, said it had always struck him as odd that the committee had to accept the decision of a bench of lay magistrates in this country but not the decision of the High Court of Australia confirmed by the Court of Appeal in Australia "There are so many absurdities," he remarked

Mr Taylor replied that there were grounds for excluding all courts which did not try cases by the law of the United Kingdom In the case of courts-martial, there could not be any grounds for excluding this offence if it was tried in Malta and including it if it was tried in Plymouth, or, as might happen in wartime, if the offence was committed in Plymouth and the trial took place in Malta

Mr Widgery, replying to the submission, said "We are dealing with offences against the law of the land It is not a matter of Naval discipline nor of the rules of the Turf" The Legal Assessor advised the committee that this was a conviction within the meaning of the Medical Act of 1956, and the Committee, accepting this advice, found the convictions proved

Mr Taylor said that Dr Lennan had the misfortune to be a homosexual It was not a crime to be a homosexual the crime was to break the law There was no suggestion that Dr Lennan had committed any other offences at other times, there was no question of seduction or abuse of his position as an officer, and to all intents and purposes these acts were committed by consenting adults in private Mr Taylor read a medical report which stated that treatment should allow Dr Lennan to control his impulse

The Chairman announced that the committee took a grave view of Dr Lennan's convictions, which they regarded as deplorable in a medical practitioner, but were prepared nevertheless to take into consideration the testimonials and representations submitted on his behalf They would postpone judgment for two years, but would expect him to appear before them at the end of one year

ADDICTION TO DRUGS

The committee had two practitioners before them who had been taking pethidine

John Galbraith Mackay Anderson, registered as of Braddons Hill House, Torquay, Devon, L M S S A, through his counsel, Mr E B McLellan, instructed by Messrs Le Brasseur and Oakley, solicitors to the Medical Protection Society, admitted a series of convictions, of which the latest was last February, when he received concurrent sentences of six months' imprisonment for driving a motor-car when under the influence of drink or drug

Mr McLellan said that as a medical student Dr Anderson had had prescribed for him substantial doses of pethidine, which relieved his asthma but laid the foundation for the addiction he had since acquired He did struggle against this, but once in a way he took the drug, and that made him more open to the influence of alcohol In 1956 he had entered hospital as a voluntary patient, but afterwards, as a locum tenens, he had had access to drugs, and their availability triggered off the addiction When he left prison he would like to enter a home for further treatment

The committee directed that Dr Anderson's name be removed from the Register This is subject to appeal

John Adams MacDougall, registered as of 34, Liberton Brae, Edinburgh 9, M B Glasg (1934), had been found guilty at Edinburgh Sheriff Court in January of procuring dangerous drugs contrary to the Dangerous Drugs Regulations In a letter he said that his psychiatrist advised him in future to avoid general medicine and general practice Since leaving hospital last March he has been working in a garage repairing motor-cars, which his psychiatrist described as "an essential part of rehabilitation from his pathological condition" The committee postponed judgment for a year

A practitioner who had morphine suppositories for a fistula later became addicted to morphine He is *James Joseph O'Reilly*, registered as of 4, Danygraig Road, Risca, Monmouthshire, M B N U I (1925), who admitted a conviction under the Dangerous Drugs Act

Mr Widgery stated that Dr O'Reilly had pleaded guilty to a number of other charges under the Dangerous Drugs Regulations, in respect of which he was put on probation for two years, with a condition that he should spend six months as an inpatient and six as an outpatient (There had been an earlier probation order, in 1954) He was at present an inpatient, and his authority had not been withdrawn by the Home Office Dr O'Reilly was represented by Mr Taylor on behalf of the Medical and Dental Defence Union of Scotland

Dr John Weir Crichton, of Chepstow, said that his junior partner and he, though not needing an assistant, were willing to take Dr O'Reilly in "if he comes to me he will have work to do and companionship" Both Dr Crichton and Dr O'Reilly would prefer that his authority should be withdrawn

The committee postponed judgment for a year

FAMILY PLANNING

AT the annual meeting of the Family Planning Association, held in London on June 7, SIR RUSSELL BRAIN, the president, surveyed the family-planning movement as it affected world population and its operation in this country

Speaking of the three scientific revolutions—in health, industry, and agriculture—Sir Russell said that, though there might be no inherent reason why the human race should not in the long run be able to solve its population problems, the complexity of the issue involved did not encourage anyone

"to think that the task of increasing the food supplies of the world until every human being has enough to eat can be carried out quickly enough to make any practical difference for a long time and we must remember that an inadequate diet means not merely being hungry or having insufficient energy for physical requirements, let alone the activity of the mind, but it often means in practice suffering from one or more of the various deficiency diseases which result from an inadequate or an unbalanced diet We are forced to the conclusion, therefore, that even if mankind, especially those in nations with power and authority, can be made aware of the problem and stimulated to seek its solution, and—a further big if—if the nations of the world can achieve a greater degree of international cooperation for the welfare of humanity than they have succeeded in achieving in most matters in the past, only the control of population growth can shorten the time which it must take for food supplies to catch up with the needs of humanity"

These facts, said Sir Russell, are forcing upon many people a reconsideration of the whole question of conception control He referred to the Warren report (*The Family in Contemporary Society*) prepared by the Church of England Moral Welfare Council for the forthcoming Lambeth Conference at the behest of the Archbishop of Canterbury As the report pointed out, there was nothing Christian in the suggestion that so-called "natural checks" should be left to exercise their own restraint upon population—that men and women and infants should be left to die and pestilence should walk unchecked, or war or abortion take their toll Sir Russell went on

"I should like to say, if I may, how encouraging it is not only to find a group of religious people prepared to examine this question afresh, but also recognising that it needs to be examined in the light of all the new knowledge which biology and psychology can throw upon it, recognising moreover that it raises questions of great difficulty in which there is room for more than one opinion"

Commenting on the historical progress in the attitude of the Church of England and other religious bodies, Sir Russell said

"It is odd that many of those who take the highest possible view of man should insist on regarding his sexual life from the lowest standpoint—that is to say, as justifiable only in terms of a biological activity which he shares with animals, namely its reproductive function Surely there is by now ample evidence in many spheres besides the sexual of how much man owes to his ability to transmute what are basically physical activities into embodiments of spiritual values It is the recognition of this which gives the Warren report such outstanding importance"

Turning to the work of the Family Planning Association in this country Sir Russell said

"But the needs of the world at large should not and do not compete with our responsibilities at home, and here we face a growing demand for our help I believe that we have a particularly valuable contribution to make to medical education of which the students unfortunately are often more aware than their teachers Why is this so important? Because family planning has come to stand for a positive ideal People have come to us not only for advice about spacing their children but because they need treatment for infertility, and because of physiological difficulties in their married lives and the psychological difficulties which are apt to spring from them Family-planning clinics, therefore, are making a most valuable contribution to the happiness and stability of married life All medical students should have the opportunity of learning how they can help their future patients in these matters, and that calls for organised and coordinated teaching in which the gynæcologist, the genito-urinary surgeon, and endocrinologist, and the psychiatrist should work together"

AWARD TO DR BAKER

Dr A S Parkes, representing the Oliver Bird Trust, presented to Dr J R Baker a special Oliver Bird medal for his contribution to research in contraception when he was associated with the Birth Control Investigation Committee Dr Parkes said the experiments Dr Baker undertook at that time were the first of their kind in a recognised laboratory in this country, and he was responsible for discovering the remarkable spermicidal powers of phenylmercuric acetate

NEEDS OF THE TEACHING HOSPITALS

Sir **Harry Platt**, at the annual meeting of the Sheffield United Hospitals on April 23, pointed out that medical science cannot stand still Diagnosis and treatment must be continuously advancing both in accuracy and in safety The "precision tools" of the laboratories, on which the practice of modern medicine is coming more and more to rely, are increasing in number and complexity "Thus we see the growing edge of knowledge on which the leading hospitals stand They cannot retreat If they are to go forward with confidence and enthusiasm they must be reassured that the sinews of war will not be withheld from them "

In the early days of the National Health Service it was hoped that the patching up of obsolescent structures would be a temporary affair, and that the epidemic of new hospital construction which has swept the North American Continent, Scandinavia, Switzerland, and more recently France and Germany, would spread to Great Britain "This has not happened, and we have been compelled to contemplate another long period practising 20th-century medicine in 19th-century structures" Despite physical and financial handicaps, British medicine so far retains a position of leadership, but a sense of frustration prolonged indefinitely must in the end handicap progress by limiting the freedom to experiment which is the lifeblood of medical science

Can we, Sir Harry asked, during the next ten years expect to see released from central Government funds, year by year, sums which will enable us both to remedy the physical defects in our hospital services and to provide for the ever-expanding needs of scientific medicine? It is estimated that for 1958–59 the gross expenditure on health services will be £736 million, of which £421 million will go to the hospitals "Will £421 million give us all that we need for our hospitals? It seems unlikely If this sum or its inflated equivalent is to represent a 'squeeze in perpetuity', what then? The difficult problem of deciding on priorities within scanty budgets will continue to dominate the picture" But there is a time-limit to the enjoyment of such austerities The Minister of Health has suggested that the upgrading of the non-teaching hospitals is an important priority "This may be good news for regional hospital boards but not so good for boards of governors, and for the universities, if they feel, as they should, an acute sense of responsibility for the structural quality of the teaching hospitals as apart from their staffs "

"We therefore face what to me is an inescapable conclusion—that for their special requirements in the future the hospitals must not only be set free, but must be encouraged, to seek additional sources of finance outside the central Government budgets of the N H S For the teaching hospitals this should be a welcome return to old practices and in keeping with their long heritage In appeals to the community, to industry, and to philanthropic individuals they would thus behave as do the universities Such efforts might enable us to see in the space of a few years several new teaching hospitals in this country, each embodying completely novel features—i e, hospitals designed specially for the purpose of teaching the undergraduate"

Addressing the meeting earlier, Alderman A Ballard, chairman of the Sheffield board of governors, quoted the remark of the House of Commons' Select Committee on Supplies that "until the standards of non-teaching hospitals reach a significantly higher level, the allocation of development and improvement money to teaching hospitals should continue to be strictly limited" It would be absurd, he said, for the teaching hospitals virtually to mark time until every other hospital caught up with them On the industrial front in Sheffield he had been seeing how the challenge of this age of *science and automation is being met* "There could easily be a catastrophic fall in our standard of living if we did not keep in the forefront in these matters It is equally true that we should fall behind in the field of medicine, surgery, nursing, and so on if the teaching hospitals had to await the raising of general standards"

Medicine and the Law

On the Soup

A WOMAN teacher of the blind, while visiting a hospital in the course of her duties, slipped at the foot of a flight of stairs on a patch of soup which had spilled from a food trolley while an orderly was pushing it to the wards She suffered severe leg injuries, and brought an action against the hospital management committee for breach of the duty owed by the occupier of premises to her as an invitee

The law as laid down in 1866 is that such a visitor is entitled to expect that the occupier will use reasonable care to prevent damage from an unusual danger of which he knows or ought to know The management committee denied negligence They admitted that soup had been spilled At the trial the orderly said that the soup, carried in a container, spilled about once or twice a week, that on this occasion, as soon as he had discovered it when he pushed the trolley aside he had gone to get a cloth to mop it up, and that the accident had happened during the 30 seconds that he was absent

The trial judge found that there had been no negligence The plaintiff appealed, and the Court of Appeal dismissed her appeal

Lord Justice **Hodson** said that the submission for the plaintiff was that the orderly ought, before going for the cloth, to have taken the obvious precaution of putting the trolley over the soup in order to comply with the legal duty owed to an invitee as laid down in Indermaur *v* Dames in 1866 The first question was whether there was here a danger, and in negligence cases it was relevant to consider the extent of the danger This was not a very acute danger, for the risk of slipping on floors was always present, and spilling a little soup occasionally could not properly be described as negligence Thus the question was whether the orderly's failure to take the obvious precaution of covering the patch with the trolley while he went to fetch the cloth could be treated as negligence If the soup had been left there a long time there would have been no doubt about the negligence But here, as soon as it was discovered, the orderly, instead of doing what the ideal citizen would do by putting the trolley over the soup, had gone straight off to get a cloth His Lordship did not think that he had fallen below the standard of care of the ordinary reasonable man The chances of accident were not very high The appeal should be dismissed

Lord Justice **Morris** said that he had felt difficulty over the case, for there was much to be said for the view that the reasonable man would have thought of the simple step of putting the trolley back over the soup once he knew it had been spilled at a place where people passed up and down fairly often and where anyone descending the stairs would put his foot But the question was one of fact and degree, and as his Lordship's brethren thought that the trial judge's conclusion was correct he would not dissent from their judgments

Lord Justice **Sellers** said that to treat this little spill of soup as if it were a hole or something of such obvious danger that it required protection would be wrong He accepted the trial judge's judgment without criticism

GRIFFITH *v* SALFORD HOSPITAL MANAGEMENT COMMITTEE *Court of Appeal* Lord Justice Hodson Lord Justice Morris, and Lord Justice Sellers June 3, 1958 Counsel and solicitors C T B Leigh (I Edwin Monks & Co, Manchester), A K Hollings (Bower Cotton & Bower for Slater Heelis & Co, Manchester)

M M HILL
Barrister-at-Law

Congresses

GASTROENTEROLOGY

The World Congress of Gastroenterology, held in Washington, D C, on May 25-31, under the chairmanship of Dr H L Bockus (Philadelphia), was attended by some 1700 delegates from 51 countries Symposium panel discussions covered five topics—peptic ulcer, malabsorption syndromes, nutrition and its effect on the liver and pancreas, intestinal infections and infestations, and gastric carcinoma—and many other original contributions covered other aspects of gastroenterology

Peptic Ulcer

Epidemiological aspects of peptic ulcer in Great Britain were described by Dr F Avery Jones, who had compared the clinical incidence of peptic ulcer after interviewing 6047 members of the public with ulcer occurrence in a survey of 7722 necropsies from nine different medical centres in the country An almost exactly similar estimate of ulcer frequency was obtained if incidental ulcers discovered in patients dying in hospital from causes other than ulcer were compared with the clinical series, while numbers of active ulcers demonstrated at necropsy closely paralleled the percentage of patients having recent clinical symptoms

In the same forward-planned concurrent necropsy survey in 1956, Dr Geoffrey Watkinson was able to demonstrate a significantly increased prevalence of most types of chronic ulcer in men and to a lesser extent in women in northern as compared with southern towns in England and Scotland where ulcers caused more deaths and were found by chance significantly more often Ulcer frequency was highest in York, Leeds, and Glasgow and lowest in Oxford and London Whether these clearcut differences reflected differing dietary, occupational, or smoking habits was not determined

Regional differences could even be demonstrated in the same district, as was shown by Dr C N Pulvertaft, who in a population survey conducted in York between 1952 and 1956 demonstrated that both gastric and duodenal ulcer, in both men and women, was commoner in the city-dweller than in the countryman from the surrounding rural area These differences did not seem to be due to social status, age differences, or smoking habits, but it was found that the sugar consumption of the ulcer patient was significantly greater than that of controls in both areas, and significantly greater in town than in country Whether this represented a causal or aggravating factor had not been established Ulcer frequency in Great Britain could be correlated with social class, lower income groups containing a significant excess of gastric-ulcer patients Familial factors seemed of importance in that ulcers occured two to three times more often in the relatives of ulcer patients—an aspect also stressed by Dr J J Dubarry (France)

Genetic factors in relation to A B O blood-groups seemed to determine ulcer site in the patient with chronic gastric ulcer, in 1500 ulcer patients analysed by Dr B P Billington (Australia), ulcers in the area occupied by the fundic glands were associated with blood-group O, whereas ulcers in the prepyloric area contained a significant excess of group-A individuals Duodenal ulcers were more likely to occur in responsible executives, and agricultural workers seemed least likely to be affected Studies undertaken by Jones and Doll incriminated smoking as a possible factor in ulcer occurrence and in delayed healing When the smoking habits of ulcer patients and controls were compared, there were substantially smaller proportions of non-smokers or of very light smokers among ulcer patients of each sex, proportions being even smaller in gastric-ulcer patients The rate of healing of gastric ulcers could be significantly accelerated if smoking was stopped

Surprisingly similar data on ulcer prevalence and disease pattern in America were presented by Dr S M Jordan, and the frequency and clinical features of ulcer in Austria (Dr R Boller), Mexico (Dr J M De La Vega), Brazil (Dr G Siffert), Switzerland (Dr B Wissmer), India (Dr P Raghavan), Japan (Dr T Kurokawa), and the Middle East (Dr J Kleeberg [Israel] and Dr D Munzer [Syria]) were enumerated Ulcer was revealed as widespread throughout the world, the disease pattern varying from place to place, in age and sex distribution, in the types of ulcer observed, and in the type of complications In this respect a report on gastroduodenal ulcer at high altitudes in the Peruvian Andes by Dr G Garrido-Klinge was of particular interest In a population of 17,500 miners working at an altitude of 12,000–16,000 feet, ulcer recurrence showed a low overall frequency of 0 7%, an increased tendency to hæmorrhage, which occurred in 53% of all ulcer patients, and an excessive preponderance of gastric ulcer, which occurred twenty-six times more commonly than did duodenal Ulcer frequency in nearby Lima at sea-level conformed more nearly to other parts of the world where the usual excess of duodenal ulcer was observed Circulatory changes and plethora induced by the high altitude were thought to be the likely explanation for this unusual pattern

Sudden changes in dietary habits were thought by Dr A Lambling to explain the increase in the prevalence of gastric ulcer in France in 1942 and 1943, when rations, particularly of protein, were at their lowest Resumption of normal feeding habits after the war led to increases in duodenal ulcer, the disease reverting to the pattern observed before the war Dr Geraldo Siffert did not feel that the "awful lot of coffee in Brazil" had affected ulcer frequency in that country

Possible hormonal factors in ulcer production were discussed by Dr S J Gray (U S A) The role of the hypothalamic-pituitary-adrenal mechanism was evaluated in relation to the peptic-ulcer reaction Steroids were shown to increase gastric acid and peptic output, to increase blood and urinary pepsinogen, to decrease the mucus protective barrier, and to impair tissue healing over a period of three to four weeks, all of which might determine ulcer formation The rarity of ulcer and the low urinary pepsinogen levels in hypofunction of adrenals or pituitary were stressed, but ulcers could be induced in these patients after steroid therapy While the urinary output of ketosteroids did not differ from normal in the ulcer patient, submaximal stimulation by corticotrophin in these patients induced a significantly greater response than in the normal, suggesting that they reacted excessively to stress

The relation of pancreatic endocrine function to peptic ulcer was elegantly described by Dr D W Elliot and Dr R M Zollinger (U S A) 75 examples of the syndrome described by these workers in 1955 had now been reported The syndrome comprised severely progressive peptic ulceration, which did not respond to surgical, medical, and radiation therapy, and gross gastric hypersecretion associated with a non-secreting β-cell adenoma of the pancreas A visible tumour in the pancreas should be locally excised and total gastrectomy performed, multiple adenomas or occult functioning metastases in a gland of normal size might make it necessary to do a partial or total pancreatectomy in cases where adequate surgery had failed to prevent ulcer

While much of the mosaic comprising the pattern of ulcer disease throughout the world was filled in, and many ætiological factors were identified, the final cause of peptic ulcer remains unclear, but it was felt that widespread epidemiological surveys would help to identify the elusive final causal factors

Malabsorption States

Causal factors in the production of the malabsorbative state were classified by Prof A C **Frazer** (Britain) as (1) conditions without enteropathy where a lack of pancreatic secretion determined defective intraluminal phase of absorption, and (2) conditions with enteropathy where the change might be induced by gluten intolerance, by folic-acid deficiency, by changes in intestinal flora, or by organic changes in the intestinal tract or wall or mesentery In gluten-induced enteropathy dietary wheat caused the syndrome, which disappeared on a wheat-gluten-free regime, only to relapse when gluten was reintroduced While acid hydrolysis and deamidation removed the deleterious effects of the compound, these persisted after peptic and tryptic digestion, and wheat gliadin and an autoclaved peptide gluten fraction would both induce the syndrome

The importance of wheat sensitivity was also stressed by Dr D H **Anderson** (U S A) and by Dr H A **Weijers** and Dr J H **Van de Kamer** (Netherlands), the latter workers had shown that patients with steatorrhœa reacted to the administration of wheat gliadin by an abnormal rise in blood-glutamine level Folic-acid deficiency was an early and prominent feature of tropical sprue, which induced temporary reversible changes in the intestine, in many patients correction of the deficiency induced permanent remission, but in others severe steatorrhœa persisted Changes in intestinal flora might determine some of the characteristics of the stools in the malabsorption syndrome, in view of the frequent dramatic responses to antibacterial therapy in patients with tropical sprue

This factor seems of little importance in the cœliac syndrome, as was beautifully demonstrated by Dr **Charlotte** M **Anderson** (Australia), who found no quantitative differences in bacterial flora in specimens obtained by intubation of the small intestine between normal children and those with malabsorption and steatorrhœa Rancid dietary fats ingested by Service personnel in Hong Kong were thought to have initiated the sprue syndrome in previously healthy young adults on a few occasions Organic enteropathies induced malabsorption in regional ileitis, Whipple's disease, scleroderma, gastrocolic fistula, and the anastomotic and loop syndrome When these various types of syndrome had been identified, few cases remained for which the term " idiopathic steatorrhœa " might be retained

The clinical behaviour of sprue in the United States was ably described by Dr E E **Wallaeger** on the basis of 400 patients seen at the Mayo Clinic since 1930 The pattern of tropical sprue in Cuba appeared to have become strikingly milder when the type of disease seen between 1927 and 1937, when a florid glosso-entero-anæmic diarrhœal disease occurred, was compared with that in the past decade, in which an incomplete mild frustrated type of disease was observed This was thought by Dr F **Milanes** (Cuba) to be due to improved individual constitutional resistance coinciding with more adequate dietary intake

One of the most significant advances in this field has been the confirmation that temporary or permanent structural changes in the intestinal mucosa frequently cause or complicate the malabsorption state This change, described by Paulley in 1952 and 1954 in fresh operative specimens, has been confirmed and its significance reassessed by the development of a small intestinal-biopsy instrument by Dr **Margot Shiner**, who in conjunction with Dr I **Doniach** (Britain) described the application of this technique to patients with non-tropical sprue. Partial or complete atrophy of the intestinal villi, with degenerative changes in the surface columnar epithelial layer and cellular infiltration, was observed This change, which inevitably accompanied idiopathic steatorrhœa and the cœliac syndrome, was irreversible even though therapy induced clinical remission The changes did not occur in symptomatic steatorrhœa complicating gastrectomy or pancreatic disease In steatorrhæas complicating the folic-acid deficiency of tropical sprue or in megaloblastic anæmia, structural changes in the intestinal mucosa were reversible by appropriate therapy

Similar changes in the distal small bowel were thought to form the basis of cyanocobalamin and folic-acid deficiency in idiopathic steatorrhoea in combined hæmatological and absorbative studies undertaken by Dr D L **Mollin** (Britain) It was now possible to demonstrate Whipple's disease by this method in place of laparotomy, which was formerly required

A perhaps more convenient device for intestinal biopsy had been developed by Dr W H **Crosby** (U S A) This consisted of a metal capsule 11 × 17 mm containing a rotating spring-activated knife which was triggered by suction when the intestinal mucosa completely occluded the biopsy orifice The capsule was held captive on a fine polyethylene catheter which served both to apply suction and to retrieve the capsule when the biopsy specimen had been taken This capsule had the advantage of being easy to swallow and of penetrating deeper into the small bowel than had been previously possible It had the disadvantage that only a single biopsy specimen could be taken, but multiple capsules could be swallowed in tandem and simultaneous biopsy specimens obtained at different levels

Several papers described the use of isotope-labelled fats, fatty acids, and protein in patients with malabsorbative states (Dr D **Sandweiss** [U S A], Dr C **Wilmer Wirts** [U S A]) This test emerged as a valuable one in the diagnosis of steatorrhœa and its distinction from pancreatic disorders

In an intensive study of normal and abnormal fat absorption by Dr R **Blomstrand** (Sweden) ^{14}C-labelled fatty acids had been fed to patients and its content simultaneously compared, in intraluminal specimens obtained by intubation, in lipids of the thoracic-duct lymph cannulated by a new technique in man and in the fæcal fats Differences in the absorption of saturated and unsaturated fatty acids were demonstrated, furthermore it was found that a part of the unabsorbed oleic acid had been hydrogenated in its passage through the alimentary tract. Diet and synthesis by intestinal microorganisms seemed quantitatively the most important sources of fæcal fatty acid

The last significant advance in this field was the introduction by Dicke in 1950 of the gluten-free diet for the treatment of the sprue syndrome While its value for cœliac disease was soon demonstrated, its value in the adult form of idiopathic steatorrhœa has only recently been established Dr J M French (Britain) discussed his experiences with the gluten-free diet in adult idiopathic steatorrhœa In 31 of 44 patients remissions had followed its use, these were characterised by weight gain, well-being, control of diarrhœa, and a return of fæcal fats and blood findings to normal Reasons for failure were hard to identify and were unrelated to sex differences, to age or duration of disease, or to previous cœliac disease. As the response to the diet was often slow, taking thirty to a hundred days, therapy should be continued for at least six months before failure was admitted Avitaminosis, anæmia, and the presence of a complicating bacterial enteritis might be further causes of failure Although varied opinions were expressed as to the merits of the diet in relation to fat restriction and to steroids, the diet seemed to be internationally accepted as a significant advance in the therapy of the sprue syndrome

Regarding the steatorrhœa complicating small-bowel resection in man, Dr M H Kalser and his co-workers (U S A) found that in patients in whom massive resections (8–10 feet) had been performed, where jejunum had been anastomosed to ileum only minimal steatorrhœa ensued, but in all cases where terminal ileum had been removed and anastomosed to colon severe steatorrhœa was observed Resections of 4–5 feet of small bowel did not cause steatorrhœa, regardless of the site of resection or type of anastomosis These findings emphasised the importance of terminal ileum and ileocæcal valve in normal fat and protein assimilation

The fact that in most instances the term " gluten-induced enteropathy " can be substituted for the term " idiopathic steatorrhœa " is a measure of the extent to which knowledge has advanced in the past decade, in which the causal factors, pathology, and effective treatment have been largely identified

Influence of Nutrition on Liver and Pancreas

The researches on the effects of lipotropic factors on liver-disease in Sir Charles Best's laboratory were reviewed by Dr G Wilgram (Canada) Although choline deficiency induced in primates fatty accumulation in the liver closely resembling kwashiorkor in man, it had not been found practicable to perform the crucial experiment which would implicate choline as the likely cause of the condition This would involve the administration of a diet with a borderline protein content, sufficient in calories, and low in choline, and it had not been found possible to devise a suitable diet for this purpose

In France Prof J Caroli has established a definite statistical relationship between the average individual consumption of alcohol and the development of cirrhosis Mortality due to cirrhosis fell by half in the period of the German occupation when alcohol was scarce A controlled investigation into the relation of individual alcohol intake to cirrhosis in three French towns revealed that wine consumption under 1 litre daily never induced cirrhosis, whereas an intake of over 2 litres daily invariably did so The fact that 1–2 litres daily induced symptoms in 40% of subjects suggested that some individual susceptibility was necessary for the development of the condition Deficient nutrition and diet were often contributory, and women seemed more likely than were men to develop symptoms Alcohol administered experimentally to animals had not consistently induced fatty change

Dr C S Davidson had found that in Boston, Mass , hepatic cirrhosis in men of 55–64 was the fourth commonest cause of death When the clinical pattern of cirrhosis in Boston, which was due most often to alcohol, was compared to that in London, England, where alcohol was rarely a cause, important differences emerged Predominantly alcoholic cirrhosis was associated with a poor dietary intake, vitamin deficiencies, jaundice, and symptoms of alcohol withdrawal were common Dupuytren's contracture and parotid enlargement were often seen, anæmia was uncommon but leucocytosis was usual The disease ran a fluctuant course but remained potentially reversible for a long time before hepatocellular failure supervened In non-alcoholic cirrhosis, by contrast, appetite was usually maintained, jaundice was rare, and a progressive course associated with anæmia and leucopenia was the rule Chances of recovery were small and the symptoms of portal hypertension were more prominent

The relation of primary liver cancer to underlying nutritional factors was described by Dr C Berman (South Africa) This form of malignant disease was one of the rarest forms of carcinoma in Europe and the Western hemisphere It was remarkably frequent among the native inhabitants of Africa and certain parts of Asia, indeed in the Bantu races and among the Indonesians it was the commonest form of internal cancer While the ultimate cause of liver cancer was unknown, it was becoming increasingly apparent that nutritional and environmental factors were important in its production Known carcinogens such as butter-yellow would readily induce liver cancer in laboratory animals, this was usually preceded by massive fatty necrosis of the liver, cirrhosis, and liver damage, and the frequency of its production could be modified by diet Indeed, in some animals liver cancer had been induced by deficient diet alone In man it seemed likely that prolonged or cyclical dietary inadequacy, so prevalent in Africa and Asia, frequently produced hepatic fibrotic lesions associated with primary liver cancer It was also possible that hepatotoxic or carcinogenic agents might be present in the food or beverages of the afflicted populations

Epidemiological aspects of acute hepatitis in Chile were described by Dr H Ducci While outbreaks of infective hepatitis in children were common in Chile, secondary infection in the adult was rare This, in conjunction with abnormal liver-function tests in apparently normal individuals, suggested that many of these patients must have had subclinical attacks of the disease in childhood, and that the majority of cases in adults were examples of inoculation hepatitis Nutrition did not seem to play a part in the spread or severity of the attacks of hepatitis

Changes in the liver and pancreas in kwashiorkor as observed in Guatemala were described by Dr N **Scrimshaw** Fat was deposited initially in the peripheral parts of the hepatic lobules, and later throughout the whole parenchyma reticulin proliferated While with appropriate therapy fatty deposits would disappear in seven to twenty-one days, reticulin proliferation persisted Pancreatic fibrosis with atrophy of the acini and collapse of the reticulin were not uncommon accompaniments of the disease, the pancreatic islets being spared until the terminal stages These pathological changes were accompanied by evidence of functional pancreatic insufficiency Although associated parasitic and dysenteric infections occurred in patients with kwashiorkor, these infections were not more prevalent than in the general child population and did not seem to be a causal factor in the production of the disease

The effects of chronic malnutrition on liver disease in Mexico and in the West Indies were reported by Dr B **Sepulveda** and Dr S **Zubian** (Mexico) and Dr J C **Waterlow** (Jamaica) Dr Waterlow had studied the behaviour of the liver enzymes in deficiency states Only cholinesterase seemed to be affected in malnutrition, levels of transaminase and dehydrogenases remaining normal

Nutritional liver and pancreatic disease in Australia was described by Dr I J **Wood** In Melbourne, although malnutrition was uncommon, it was detected in a third of all patients attending a gastrointestinal clinic Alcoholism, organic disease of the gastrointestinal tract, food fats, and psychiatric disturbances were the common causes of the deficiency Dietary inadequacies induced fatty and later cirrhotic changes, which remained reversible for long periods before hepatic coma developed Arginine seemed promising in the treatment of hepatic coma Pancreatic disease was produced when malnutrition was associated with alcoholism, and this combination had been the cause in 17 out of 90 cases of acute or chronic pancreatitis Other common causes of pancreatitis were mumps, systemic vascular disease, gallstones, hyperlipæmia, pregnancy, and hæmochromatosis Although the incidence of parasitic disease, particularly roundworms, was high it seemed unlikely that these contributed to the production of the pancreatic or liver lesions

While this symposium produced valuable information on liver disease throughout the world, much still remains to be identified—particularly the enzymatic changes in the liver cells which initiate the structural damage

Intestinal Infections and Infestations

Perhaps the most important fact that emerged from this symposium was the uncertainty as to the significance of pathogenic organisms and parasites when found in the bowel or stool

Infection

Dr **Erwin Neter** (U S A) emphasised that mere isolation of *Escherichia coli* from the fæces of children did not prove that diarrhœa was due to this organism, special serotypes—notably O 111 B 4, O 55 B 5, and O 127 B 7—could be incriminated since they were found in infants with enteritis, were rarely present in health, and would produce disease if fed to volunteers, an enterobacterial hæmagglutination test revealed antibody formation in infections of this nature, which could be controlled by neomycin Dr Neter had seen a case of diarrhœa infested with shigella and *Esch coli* which antibody reactions proved to be due to the shigella He went on to emphasise the possibility that viruses of the Echo and Coxsackie groups might be the underlying cause in some epidemics of diarrhœa in the newborn

Prof **Nanna Svartz** (Sweden), though considering ulcerative colitis to be infective in origin, did not regard dysenteric organisms, and in particular shigella, as a cause, and suggested that when these organisms had been associated with the disease, as in Felsen's series, they might have been secondary invaders She did, however, believe that an attack of dysentery could so sensitise the colon that it could later become vulnerable to its normal flora, which increase in number and virulence following dysentery

Dr **Joan Taylor** (Britain) held that the villain of the piece remains undetected in a large proportion of diarrhœal diseases, and that the serotypes of *Esch coli*, O 26, O 55, and O 111, like the poor, were always with us, and were pathogenic the world over, whereas O 127 waxed and O 128 waned in their pathogenicity, forming with others (O 117, O 86) a group only intermittently capable of causing disease No differentiation could be made on clinical grounds alone between coliform, salmonella, and shigella infections, all of which had become milder, classification could only be made bacteriologically In Britain shigella infection was almost always due to *Sh sonnei*, there being 43,000 cases each year, and few were due to *Sh flexneri*, these being in mental institutions Each year there were 6000 cases due to salmonella infection, in 75% of which the organism was *Salmonella typhimurium*, this gained access in protein foods imported for man and animals

Dr W H **Dearing** (U S A) doubted whether *Staphylococcus aureus* could be held to account for all cases of pseudomembranous enterocolitis, since of 19 deaths from this disease in 11 cases no staphylococcus could be found in the bowel at the time of death, contrariwise in 4 necropsies in patients with staphylococcal enteritis who died of other causes, no ulcerative or pseudomembranous lesions were observed in the intestines

Infestation

The mere presence of *Entamœba histolytica* in the stool must not be taken as evidence of clinical amœbiasis Dr R **Elsdon-Dew** (South Africa) pointed out that in Britain, although 10% of the population were infested with *E histolytica*, amœbiasis was virtually unseen, whereas in Durban the disease was rife though the prevalence of infestation was no higher The manifestation of disease in the presence of the parasite was in some way associated with urbanisation and industrialisation, for the incidence in Coloured South Africans was higher in towns Diet appeared important, the wheat-fed being more susceptible than those eating rice, the rural Negro on moving to town changed his diet to one based on high-extraction wheat flour and sugary drinks This caused a change in intestinal bacterial flora and permitted the amœbæ already present to become parasitic—a situation which could be reversed by attacking the bacteria with antibiotics Dr Elsdon-Dew pointed out that symptoms were commonly ascribed to amœbiasis in error, simply because *E histolytica* was found in the stools He asked Should antiamœbic treatment be given whenever the protozoan is found?, and in the panel discussion which followed it became clear that others are asking the same question

Dr R Armas Crus (Chile) raised the problem of treatment Evaluation was difficult both clinically, since many patients had no symptoms, and from the stools, since the parasites might disappear spontaneously from the stools and reappear later In a controlled investigation into the efficacy of various forms of antiamœbic therapy the control placebo had proved as effective as the best treatment, causing the trophozoites to disappear in 72 7%

Dr M M Brooke (U S A) was concerned with the difficulties of demonstrating *E histolytica*, particularly in the non-dysenteric cases and carriers when the distinctive trophozoites are absent Stool examinations must include a careful search for cysts He outlined methods of collection and examination and emphasised that the reliability of a laboratory depended on the skill of the microscopist Serological and complement fixation tests were not of value

In Cuba, said Dr J G Basnuevo, about 5% of people are infested with *E histolytica*, but there was considerable regional variation, the prevalence being inversely proportional to the density of the population White were more commonly infested than Coloured people, as were females than males, but liver abscess was far commoner in men than women and was usually seen between the ages of 30 and 50 (it had been observed under the age of 2)

Gastric Cancer

In this symposium emphasis was laid upon the need to detect the early cancerous and the precancerous lesions

Dr I S Ravdin (U S A) pointed out that only surgery could alter the course of the disease, and that a five-year-survival rate of 50% could be obtained in cases with no lymph-gland involvement. The outcome of operation depended more on cases being brought early to surgery than on the extensiveness of resection, indeed, total gastrectomy, in his opinion, was unsuitable At his clinic only 4% of patients submitted to palliative resection survived for five years, in contrast to 22% of those in whom resection was undertaken for cure These figures obtained after an overall operative mortality (death within thirty days) for resection of 2 8–5 7% in palliative operations and of 0 9% in curative operations He emphasised the persistent doubt regarding malignant change in benign gastric ulcers, and that X-ray evidence of healing in a gastric ulcer cannot be taken as evidence against malignancy

On the other hand, Dr W H Bachrach (U S A) in an original paper denied that there was good evidence that malignant ulcers had been observed radiologically to heal

Dr Leo Rigler (U S A) felt that the improvement in results to be expected from advances in surgical technique had now reached the limit, and it was incumbent on the radiologist to find means of disclosing cancer of the stomach at an early stage, indeed in an asymptomatic stage In a small series of 38 cases, 22 were revealed without symptoms and 16 were subsequently found to be node-free, 11 had mild symptoms with 3 node-free, and of 5 with frank symptoms all had node involvement It was therefore at the asymptomatic stage that surgery really had its chance to cure, and in 36 cases of this group in which resection was possible a 33% five-year-survival rate was achieved The task of universal routine check X-rays was too great to contemplate, but the problem could be approached by investigating those patients in whom cancer seemed especially likely to arise He had made a pilot study of 3510 patients who had either no or low gastric acid or addisonian anæmia, and compared them with 1098 controls with normal acid In the control group no cancer or polyp was revealed 36 (1%) of the 3168 patients with no acid had evidence of cancer and 80 had polyps, of the 271 with low acid, 2 had carcinoma and 2 polyps, and of the 71 with addisonian anæmia 4 had a growth and 6 polyps

The search for a chemical test to reveal gastric cancer continues, Dr Y Tazaki (Japan) has found an increase in serum-fibrinogen, but this is not specific Also from Japan came reports in original papers that the reducing power of gastric mucoprotein is increased in the presence of cancer together with an increase of amino-acid nitrogen, of a cancer "toxin" which on injection into mice decreases the liver-catalase (Dr Hachiro Sato), and of a complex mucoprotein or polysaccharide extracted from gastric juice in cancer patients which on injection into rabbits causes a fall in erythrocyte numbers (Dr Kaichiro Ogura)

Dr J Clemmesen (Denmark) pointed out that gastric carcinoma comprised about 20% of all cancers in England and the U S A , 30% in Denmark and most European countries, and 40% in the rest of Scandinavia In Denmark, as in England, size of income was inversely related to incidence of gastric cancer

Dr J Maisin (Belgium) suggested that certain foods might dispose to cancer, smoked foods in particular had a higher carcinogen content than other foods

The experimental induction of cancer in mice and rats by 20-methylcholanthrene 0 3 mg injected into the stomach wall was described by Dr H L Stewart (U S A) In rats gastric cancer seldom developed spontaneously, but the distribution in the stomach of experimentally induced tumours mimicked that in man

Ulcerative Colitis

Dr R A Sifre (Puerto Rico) described 81 cases of ulcerative colitis seen over a sixteen-year period Though the condition was less common in Puerto Rico than in temperate countries its natural history and complication-rate followed the usual pattern. No ætiological relation had been found between bacillary or amœbic dysentery and ulcerative colitis, though parasites had been found incidentally in the stools of 22 cases

Dr S C Truelove (Britain) assessed the therapeutic value of hydrocortisone applied rectally in ulcerative colitis Remission had followed instillation of the alcohol-free derivative (60–120 mg each night) in 14 out of 21 courses, and of the water-soluble hemisuccinate compound (100 mg each night) in 11 out of 18 In a controlled trial the hemisuccinate was effective on 11 occasions out of 20 courses, in contrast to once out of 20 for the blank.

Dr M B Goldgraber (U S A) had studied the pathology of surgical specimens from 76 patients and 46 necropsies Neither cryptitis nor vasculitis was predominant, but infiltration with histiocytes and granuloma formation were noted—suggesting a hypersensitivity reaction

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But all is not black, I have a first-rate boss and spend the day with sagacious and kindly health visitors The breathtaking beauty of the countryside as spring leads into summer is worth the loss of £1000 a year On the home front, too, there are compensations—no wifely grumbles about " these awful boys ", and my children are living a more normal life, making better progress at school, and acquiring a decent accent

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A busless London is a pleasant sight,
  No big red monsters there to block the light
And as the crowds pass by with hurried feet
  They see the full perspective of the street,
While at the stopping places where of late
  Long rows of heavy buses used to wait
The passing car will offer you a lift
  —No payment asked—a very welcome gift

The traffic problem now seems to be solved—
  What's that you say? *The deadlock is resolved?*
The men going back to work? Oh tell me when?
  I shall be glad to see them back again

Letters to the Editor

THE DANGEROUS WATER-STERILISER

SIR,—Much publicity has been given to the efficiency and testing of autoclaves in operating-theatres, but attention has seldom been drawn to the water or lotion sterilisers Most outbreaks of theatre infections are due to bacteria which are easily killed even by an inefficient autoclave, and in three different outbreaks which I have investigated the infection was traced to the water sterilisers

These have several danger points They consist of a tank in which water is heated by a steam coil and cooled by a cold-water coil The water entering the tank is controlled by a screw tap and is drawn off through a similar tap The water level is indicated in a glass tube connected to the tank at top and bottom An air vent and safety valve is fixed to the tank and usually a cotton-wool filter is inserted into this After the water in the tank has boiled for half an hour it is considered sterile and is cooled, but I have often found coliform bacilli and cocci in it, which were killed at a temperature of 60°C in a few minutes The water must therefore be contaminated after boiling, and the possible ways of entry are

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The first four faults are easily remedied, but difficult to spot I have seen a new installation in which the washers in every single valve were perished, but this was not noticed until a large number of postoperative infections had occurred

Faults (5) and (6) are most difficult to rectify The outlet tap may be sterilised by directing a jet of steam over it before use, and the water-level gauge can be emptied when the water is boiling and steam from the tank allowed to pass through it It is possible to produce sterile water in this way, but it is not absolutely safe and only a bottled supply of autoclaved water can be guaranteed to be sterile

Central Pathological Laboratory,
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PHYSICAL CHANGES IN THE PROLAPSED DISC

SIR,—In your annotation of June 7 you outline one of the difficulties in understanding disc disorders—namely, how to reconcile the theory that pain can be caused by swelling of the disc with the observed fact that at operation the protruded disc material is stringy and desiccated

If a practitioner is to reassure his patients by explanation he must be given a working hypothesis May I suggest the following scheme?

The normal internal turgor of the disc, as well as the episodes of abnormally high tension which I believe are the cause of lumbago, depend on the presence of a mucoprotein which has a powerful affinity for water The normal process of ageing is accompanied by desiccation of the nucleus which is presumably the result of physicochemical changes in the structure of the molecule of the mucoprotein The slow physicochemical change of normal senescence in the disc is symptomless and elderly patients are much less prone to a first attack of lumbago than are those in early middle age I suggest that a disc which is the site of acute lumbago in early middle age has gone through the physicochemical changes of senescence in a matter of days or weeks The molecular change is accompanied in its early stage by a raised affinity for water, and the swelling of the disc produces the pain and spasm characteristic of lumbago When the acute phase of the episode subsides, which is usually before the end of the third week, the contents of the disc are left in the condition of senescence This process may affect an isolated disc in an otherwise normal spine The process may cause complete degeneration of the disc, in which case the patient never has another attack of lumbago or sciatica Alternatively, the degeneration may be focal and sufficient normal mucoprotein may be left to cause further episodes of lumbago before the disc becomes finally and permanently inert

We now arrive at the concept of a disc sequestrum This is the result of focal degeneration and is the symptomless residue of a previous tension episode This is what is removed when we operate on a disc protrusion The popular idea of how this sequestrum is projected through the layers of the annulus is the simple mechanical explanation that it " slips out " or is forced out by injury This mechanism most certainly can occur, and it explains those disc protrusions which happen suddenly and without premonitory symptoms But many disc protrusions are ushered in by discomfort in the back before the full violence of the attack is precipitated by a trivial movement In these cases I believe that the sequestrum is pushed out of the disc by an episode of raised internal tension affecting the mucoprotein which is as yet undegenerate This theory explains those disc protrusions which subside with the passage of time, made tolerable by simple heat Those cases which do not subside have a disc sequestrum firmly lodged in the displaced position which has failed to retract when the internal tension of the nucleus has subsided

I should be interested to know whether biochemists or biophysicists can offer any objection to this simple creed

Department of Orthopædic Surgery,
Manchester Royal Infirmary JOHN CHARNLEY

TREATMENT OF ASTHMA AND HAYFEVER BY HYPNOSIS

SIR,—The *argumentum ad hominem* has played a declining role in scientific controversy since its heyday during the Renaissance, when forensic skill could still make up for deficiencies in other respects Science is now a discipline in which impartial inquiry may be assumed as a matter of course, and it is agreed by all concerned that if observations are accurately made and experiments are well designed as well as being capable of repetition by other workers, then their scientific validity is quite independent of the temperament, motives, religious beliefs, taste, or any personal quality of the investigator, except perhaps his sagacity His work can only be criticised on these terms, and no scientific investigator worthy of the name places any reliance on persuading his opponent with rhetoric or on driving him from the field with invective, as President Conant so aptly puts it It is possible, therefore, if not certain that the failure to understand Dr Mason and Dr Black's contribution on my part, and I was not alone in this, may be elsewhere than in my alleged emotional attitude towards hypnotism

I am sorry to see, Sir, that you number yourself among the " statistics can prove anything " school, and I am sure that this view is partly based on a misconception of the use and function of statistical methods in biological research Such a misconception is well illustrated by a remark of Dr Mason and Dr Black in their letter of May 24 where they state " it often seems that almost any *result* (my italics) can be obtained

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If a practitioner is to reassure his patients by explanation he must be given a working hypothesis May I suggest the following scheme?

The normal internal turgor of the disc, as well as the episodes of abnormally high tension which I believe are the cause of *lumbago, depend* on the presence of a mucoprotein which has a powerful affinity for water The normal process of ageing is accompanied by desiccation of the nucleus which is presumably the result of physicochemical changes in the structure of the molecule of the mucoprotein The slow physicochemical change of normal senescence in the disc is symptomless and elderly patients are much less prone to a first attack of lumbago than are those in early middle age I suggest that a disc which is the site of acute lumbago in early middle age has gone through the physicochemical changes of senescence in a matter of days or weeks The molecular change is accompanied in its early stage by a raised affinity for water, and the swelling of the disc produces the pain and spasm characteristic of lumbago When the acute phase of the episode subsides, which is usually before the end of the third week, the contents of the disc are left in the condition of senescence This process may affect an isolated disc in an otherwise normal spine The process may cause complete degeneration of the disc, in which case the patient never has another attack of lumbago or sciatica Alternatively, the degeneration may be focal and sufficient normal mucoprotein may be left to cause further episodes of lumbago before the disc becomes finally and permanently inert

We now arrive at the concept of a disc sequestrum This is the result of focal degeneration and is the symptomless residue of a previous tension episode This is what is removed when we operate on a disc protrusion The popular idea of how this sequestrum is projected through the layers of the annulus is the simple mechanical explanation that it " slips out " or is forced out by injury This mechanism most certainly can occur, and it explains those disc protrusions which happen suddenly and without premonitory symptoms But many disc protrusions are ushered in by discomfort in the back before the full violence of the attack is precipitated by a trivial movement In these cases I believe that the sequestrum is pushed out of the disc by an episode of raised internal tension affecting the mucoprotein which is as yet undegenerate. This theory explains those disc protrusions which subside with the passage of time, made tolerable by simple heat Those cases which do not subside have a disc sequestrum firmly lodged in the displaced position which has failed to retract when the internal tension of the nucleus has subsided

I should be interested to know whether biochemists or biophysicists can offer any objection to this simple creed

Department of Orthopædic Surgery,
Manchester Royal Infirmary

JOHN CHARNLEY

TREATMENT OF ASTHMA AND HAYFEVER BY HYPNOSIS

SIR,—The *argumentum ad hominem* has played a declining role in scientific controversy since its heyday during the Renaissance, when forensic skill could still make up for deficiencies in other respects Science is now a discipline in which impartial inquiry may be assumed as a matter of course, and it is agreed by all concerned that if observations are accurately made and experiments are well designed as well as being capable of repetition by other workers, then their scientific validity is quite independent of the temperament, motives, religious beliefs, taste, or any personal quality of the investigator, except perhaps his sagacity His work can only be criticised on these terms, and no scientific investigator worthy of the name places any reliance on persuading his opponent with rhetoric or on driving him from the field with invective, as President Conant so aptly puts it It is possible, therefore, if not certain that the failure to understand Dr Mason and Dr Black's contribution on my part, and I was not alone in this, may be elsewhere than in my alleged emotional attitude towards hypnotism

I am sorry to see, Sir, that you number yourself among the " statistics can prove anything " school, and I am sure that this view is partly based on a misconception of the use and function of statistical methods in biological research Such a misconception is well illustrated by a remark of Dr Mason and Dr Black in their letter of May 24 where they state " it often seems that almost any *result* (my italics) can be obtained (or refuted) by statistics" The fact is, as everyone should know, that statistical methods are used to determine the significance of experimental findings or observations and to test the validity of the hypothesis on which they are based In short, they are applied to results and not to obtain a result

Statistical methods are essential in a large proportion of biological investigations, such as therapeutic trials or studies of the effects of suggestion, because of the variability of living organisms and the sheer physical impossibility of studying the whole population If we are going to learn how suggestion works, we must have controlled studies of a random sample of the population One case just will not do The chequered history of hypnotism reveals the need for such studies and until they are carried out the wise practitioner will preserve that scepticism which is one of his marks of scientific sagacity

Dr Mason and Dr Black are not quite correct in their references to von Pirquet's "original allergy" He did not coin the term "allergy" with specific reference to old tuberculin in sensitised subjects, as they state in their letter Von Pirquet first introduced the term "allergy" in a special paper entitled Allergie,[1] the purpose of which was to devise a name for a phenomenon which far from being specific to old tuberculin was of widespread biological significance, as the following extract clearly shows

> Der Geimpfte verhält sich gegenüber der Lymphe, der Luetische gegenüber dem Syphilis-virus, der Tuberkulöse gegenuber dem Tuberkulen, der mit Serum Injizierte gegenuber dem Serum anders als ein Individuum, welches mit dem betreffenden Agens noch nicht in Beruhrung gekommen ist er ist deswegen noch weit entfernt, unempfindlich zu sein Alles was wir von ihren sagen konnen, ist, dass seine Reaktionsfähigkeit gändert ist
>
> Fur diesen *allgemeinen* (my italics) Begriff der veränderten Reaktionsfahigkeit schlage ich den Ausdruck Allergie vor

He goes on to say that he inserted this name to avoid confusion and standardise the nomenclature

London, S W 1 E J Moynahan

Sir,—The article by Dr Mason and Dr Black (April 26) demonstrates rather clearly the role of the central nervous system in controlling allergic reactions in man An experiment which should more precisely characterise the mechanism of this psychic "control" would be the effect of hypnotic suggestion on the skin reaction to histamine Would it be possible to abolish the cutaneous response to injected histamine by direct hypnotic suggestion in their patient?

Laboratory of Cellular Physiology and
Metabolism, National Heart Institute,
Bethesda, Maryland
Arnold M Katz

HYPOTHERMIA BY INTERNAL COOLING IN MAN

Sir,—Dr Khalil (May 24) describes a method of producing hypothermia in man by pumping cold water through an intragastric balloon Dr Khalil used this method in two cases in which intracranial tumours were removed surgically under hypothermia One of the two patients developed auricular fibrillation which lasted for a few hours

It seems likely that intragastric cooling might cool and irritate the neighbouring myocardium and that intragastric cooling might be more likely to cause cardiac arrhythmia than, for instance, surface cooling About one year ago I saw a patient who twice developed transient auricular fibrillation while drinking large quantities of ice water

The patient was a 31-year-old physician who had previously been enjoying good health On a warm day he had been doing moderately strenuous exercising, practising soccer A few minutes after he had finished he drank a pint and a half of ice water in the course of less than ten seconds Right away he noticed palpitations and diagnosed auricular fibrillation, which lasted for ten hours and then suddenly left him Six weeks later exactly the same thing happened, the patient again developing auricular fibrillation while drinking large quantities of ice water This time the auricular fibrillation lasted for eighteen hours, an E C G proved the diagnosis, and the patient took 0 4 g of quinidine before normal sinus rhythm was restored He has now stopped his unhealthy habit of drinking large quantities of ice water in a short time, and has had no further attacks of auricular fibrillation

St Joseph's Hospital,
Porsgrunn, Norway
Per Stavem

"THESE DYING DISEASES"

Sir,—When I noticed among my patients with gonorrhœa one with a cervicitis and another with a urethritis after penicillin treatment, a cervical smear was made and gonococci still showed in one of them

Since I could not explain this I consulted Sir Alexander Fleming after he asked me to see him, just three weeks before his untimely death He did not believe that gonococci could be resistant to penicillin and asked me to show him a culture, which I promised to do when I took a smear in both these patients after menstruation Unfortunately he died before I could deliver the cultures, but when I asked him earlier whether it would not be right to vaccinate women with live gonococci intracutaneously, when the gonococci had become resistant, his answer was, "Before one does that" (and he knew about the striking results after 10,000 of these injections in chronic female gonorrhœa) "I would like to make sure that there really are penicillin-resistant gonococci"

I believe that active immunisation with live gonococci is the treatment of choice in penicillin-resistant gonococci, and I would say more Lately, Dr Sequeira of the Royal Free Hospital has given me many gonorrhœa cultures for intracutaneous injection in these cases, as well as in rheumatoid arthritis, and the results have been very gratifying

London, W 1 A A Loeser

VEIN STRIPPERS

Sir,—I was interested to read of Mr O'Malley's "adventure" (May 31, p 1180) and also Mr Ker's account of a modified Myer's vein-stripper (May 10, p 998) I, too, have passed the small end of a vein-stripper into the femoral vein on occasions, but luckily I have never found it irretrievable Two points in technique are worth mentioning here

One is the practice of some schools to strip the vein out from above down It is rare, however, for the small end of any stripper to be passed down with ease For this method an articulated guide-wire has to be passed up first, so the potential danger still exists The guide and stripper employed is the Swanson type which has been used (optionally) in Glasgow for many years

In this way it is claimed there is less immediate anchoring effect from the tributaries alongside, and consequently less chance of the main vein tearing The steel edge of the "cup" neatly divides the branches about one inch away Mr Ker's rubber-tubing modification shows he appreciates the same principle but is unaware of the existence of the superior all-steel instrument

The other point is the type of incision used to expose the termination of the long saphenous vein I favour a vertical approach because of the greater access it affords to the tributaries Very adequate exposure is obtained using a self-retaining mastoid retractor which leaves the assistant with both hands free

The oblique skin-crease incision is in my opinion the commonest cause of failure to ligate all the tributaries This is obvious when re-operating on "recurrent" cases The vertical incision, of course, cuts across the natural skin crease, and just crosses the inguinal fold Careful closure is required with sutures not more than 1 cm apart These must also be left in for a full ten days Normally I do not use any deep sutures

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[1] *Munch med Wschr* 1906, 53, 145

Mr O'Malley does not say what approach he employed, or whether a separate incision was required With the vertical incision it can be simply extended up or down to cope with most stripper difficulties in the vicinity of the saphenous termination

Stobhill General Hospital
Glasgow

F T CROSSLING

THIRST

SIR,—Apropos of Dr Eaton's astonishment that salt depletion can give rise to a sensation of thirst (May 10, p 1021), it must be admitted that water is almost always lost as well Nevertheless, since in severe depletion the loss of salt is greater than the loss of water, the concentration of sodium in the serum is lowered and hypotonicity results

This has been commented upon by Dr O'Shaughnessy, late of Newcastle upon Tyne, in a letter in your columns[1] He noted that in the worst cases of cholera the blood loses not only a "large proportion of its water" but a "great proportion of its neutral saline ingredients" He further states that all the salts deficient in the blood "are present in large quantities in the peculiar white dejected matters" Since Dr Schmidt of Dorpat[2] has more recently confirmed these observations (he found the sodium reduced from the normal level of 3 18 g per kg of serum to 2 69 g in cases of cholera—a decrease from 139 to 117 mEq per litre), I have no reason to doubt their accuracy

That thirst occurs in cholera despite this lowering of serum-sodium is attested by Dr Latta, late of Leith,[3] who treated his patients by infusing salt solution intravenously, noting that " the poor patient, who but a few minutes before was oppressed with sickness, vomiting, and *burning thirst*, is suddenly relieved from every distressing symptom" (italics mine)

Veterans Administration Hospital,
Boston, Massachusetts

M B STRAUSS

REGIONAL DISTRIBUTION OF CONSULTANTS AND S.H.M O s

SIR,—Thank you for publishing (May 31, p 1169) the S H.M.O figures for the various regions in response to my letter in your issue of May 17 Using these figures with the previously published population figures for each region I calculated the following

Region	*Population per S H.M O (whole-time equivalents)*
Newcastle	32,000
Leeds	31,000
Sheffield	35,000
N W Metropolitan	21,000
N E ,,	28,000
S E ,,	27,000
S W ,	22,000
South Western	25,000
Welsh	24 000
Birmingham	41,000
Manchester	36,000
Liverpool	30,000

With only two exceptions the backward areas in consultant cover are also the worst off for S H M.O s—in order of backwardness, Manchester, Sheffield, Leeds, and Liverpool—which is what I suspected In other words, the lack of consultants is not even compensated by an increase in S H M O s (of the two exceptions, Newcastle has the next best consultant cover, while Birmingham is about average)

The only conclusion is that the population in the backward regions is having a poor deal in the way of Health Service facilities, whereas since they are all highly industrialised and congested parts of the country they really require better than average

As regards consultants and S H M O s in these areas, they are obviously working under conditions where they cannot give the full benefit of their knowledge and skill because the numbers they have to cope with are too large I say "obviously", because having worked in one of the best organised regions I am now working in one of the worst (according to the above figures) and therefore realise the disparity in facilities from consultants right down the line, including ancillary medical and clerical staff, almoners, health visitors, &c.

General practitioners tell me they have to wait weeks for outpatient appointments and sometimes weeks for diagnosis reports—indeed, I am surprised they get reports at all sometimes, because I find it very difficult to get a reply when I refer patients to another specialist for an opinion I feel that the basic trouble is not that of a studied discourtesy but that too few people are trying with too few facilities to do too much work for too many

As I understand that regional-board finance is on a per-capita basis, may I put in a plea for the backward areas to have a higher proportional allocation of money than the advanced regions until the medical services throughout the country are more evenly distributed?

S H.M O (EX-SENIOR-REGISTRAR)

THE NATURAL HISTORY OF CHRONIC BRONCHITIS

SIR,—We are grateful for Dr Medvei's comments last week on our paper of May 31, although, since neither of us has seen the unpublished report to which he refers, we are unable to follow his argument completely

We were aware (one of us, A.S F, from several years in the Treasury Medical Service) of some of the medical and administrative problems involved in the disposal of postmen crippled by respiratory disease and of the special circumstances in some bigger offices But we could find no evidence that any such localised anomalies in disposal materially affected the broad pattern of results in the large groupings of areas, ranked simply on the local frequency of fog, used in our study The only observations restricted wholly to the London area dealt with the timing of onset of absence because of bronchitis in relation to climate.

All occupational groups are selected but this does not mean that their experience is of no general relevance The wastage-rate because of bronchitis among postmen in different areas is quite closely related to local death-rates from that cause among all middle-aged males Nor does such selection make "controls" superfluous Without control comparisons some of the results would have been meaningless, and we believe that presumably healthy postmen are the most appropriate choice in these circumstances

It appears, however, that Dr Medvei would have us defy the usual scientific conventions by going beyond the data presented in our paper It is clear from the distribution of bronchitis frequency in adult sickness-absence records that all future invalids do not present with repeated attacks before the age of 45 Our sober assessment that these records had "some" value recognises that, taken alone, they are certainly not infallible Dr Medvei's term "exceptional" presumably derives from his experience of their use with additional clinical data—e g, on childhood disease, obtained by detailed interview

Our hesitancy about drawing conclusions on the role of smoking in chronic bronchitis resulted from the rather indirect nature of our evidence We have already referred elsewhere[1 2] to Oswald and Medvei's paper which showed that the prevalence of histories suggestive of chronic bronchitis is similar in the two sexes but only when job, place of work, and smoking habits are alike We ourselves could offer no fresh information on this important point and a further reference would have been irrelevant

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[1] *Lancet*, 1831–32, i, 490
[2] Charakteristik der epidemischen cholera gegenuber verwandten transsudationsanomalien. Leipzig 1850
[3] *Lancet*, 1831–32, ii 274.

[1] Fairbairn, A. S, Reid, D D *Brit J soc. Med* 1958, 12, 94
[2] Reid, D D *Proc R Soc Med* 1956, 49, 767

Dr Medvei is right to insist on the need for more intimate knowledge of the personal factors, which we have only hinted at Our results are based on limited if unique data We regard them simply as an indication of the importance of the questions they raise and as a stimulus to the publication of more detailed clinical studies such as those which Dr Medvei has pursued

London School of
Hygiene and Tropical Medicine,
London, W C 1

D D REID
A S FAIRBAIRN

A DRESSING FOR BURNS

SIR,—During the four years I spent in New Zealand I used a material known as 'Telfa' dressing on many patients with extensive burns This material is virtually non-adherent, and can in consequence be removed painlessly without an anæsthetic

As far as I can gather telfa dressing is not available in this country, and I find that most of my colleagues have never heard of it Is it too much to hope that some British manufacturer will produce a similar product?

'Telfa' dressing is made by Messrs Bauer and Black

Edinburgh, 8

MICHAEL WOODRUFF

CARDIO-CHARTING

SIR,—May I comment on the review of my book, *Cardio-charting*, in your issue of March 8, 1958?

It is true that many methods of clinical recording of heart auscultation have been suggested and that some are even used individually—but none are all-inclusive, nor universal in scope Each clinician uses his own personal method of charting his findings Consequently his records are either too long or too short, often they are incomplete or illegible, and occasionally these charts can be understood *only* by the author himself Whatever the merit of such charts, they are only personal and have not the quality of a standard system

It is true that constant progress is made in the knowledge of hæmodynamics—but this has nothing to do with a *method of charting* the clinically perceived acoustic cardiac phenomena, whatever their physiology

Moreover, as clearly indicated in my book, the limited clinical examples as well as the limited number of coloured illustrations were given (1) as a reminder for students of basic murmurs, well known and described in textbooks, (2) as samples of the way the method should be used when recording these and any other murmurs

Cardio-charting is not a textbook of physiology, nor a compilation of opinions

I welcome any criticism, provided it bears on the substance of the subject, but I was surprised, indeed, to find in *The Lancet* a review which had no relationship to the description of my method

Cardio-charting, as the title clearly indicates, is a method for registering uniformly all cardiac auscultatory findings in a practical and a useful way blue symbols for heart sounds, red symbols for heart murmurs The resulting permanent record is helpful not only for the examining physician himself to recollect his own past findings, but it is also helpful in promoting a mutual and universal understanding of chartings made by any physician in any part of the world, irrespective of language

New York

ARTHUR BRISKIER

*** Dr Briskier's book has served a useful purpose in drawing attention to the need for more accurate description of heart sounds and murmurs *In our view, however,* his system has few practical advantages over the drawing of sounds and murmurs in the way that many cardiologists already do, and his use of musical connotations and colour adds complications —ED L

DEATH OF A BOXER

SIR,—Before condemning what some of us believe to be the wholesome exercise of amateur boxing our profession must be sure of its facts

For example—if I may make a personal reference—I have been associated with schoolboy and R A F boxing for well over twenty years in the capacity of medical officer, examining candidates and observing them during contests The lads we deal with are nearly always good sporting types and largely through the art of boxing develop such qualities as courage, ability to keep good-tempered in the face of rebuffs from determined opponents, alertness, and efficient eye-muscle coordination I have not come across one case showing evidence of brain injury among these young amateurs, and it seems unlikely that either in school or Service such cases would escape notice for long Perhaps I have been specially fortunate, colleagues with similar or greater experience could perhaps enlighten us on this point

By all means let us have full investigations, accidents may accompany any form of physical activity and many people may get bangs on the head, but I venture to suggest that it is not advisable to generalise about the effects of such injuries pending impartial investigation I am inclined to doubt whether the effects of the ordinary "knock-out"—uncommon, by the way, in my experience in schoolboy boxing—are comparable to the results which Dr Byrom tells us accrue if the dura of an anæsthetised animal is opened and the surface of the brain touched

P R KEMP
Assistant Principal School Medical Officer,
City of Birmingham

Birmingham

SIR,—It is probable that the answer to Dr Byrom's question in the final paragraph of his letter last week is in the negative and that it would be about as futile to marshal the facts about boxing and to keep them before the public as it has been on the subject of cigarette-smoking, bronchitis, and bronchial carcinoma One of the reasons is that most of the medical profession seem to be indifferent to these evils and have given neither a lead nor an example to the laity the majority of doctors smoke cigarettes, and many attend boxing matches Only lonely and individual voices, like those of Dr Summerskill, Mr Doggart, and Dr Byrom, are heard crying in the wilderness of crass indifference

We live in an age as brutal, violent, vicious, and immoral as any of those in recorded history that preceded the Christian era, and with less excuse Boxing promoters, boxing journalists, and patrons of the prize-ring, lacking the courage of those who provide the "entertainment" but gloating nevertheless on knockouts, cut eyes, and pouring blood, are the ferocious and brutalised descendants of those who, in gladiatorial times, without mercy turned down their thumbs to make a Roman holiday It is as monstrous, wrong, and indefensible to cause gratuitous injury to the miraculous organs of the body as it would be to detonate an H-bomb without provocation, and it is as necessary for the Government of the country to enact legislation forbidding it as it was for the same authority to legislate against crime

When a sports writer on a well-known national daily newspaper can write that he feared a certain boxer had "lost his *killer* (my italics) instincts" and when feral cries of "kill 'im, kill 'im" can be heard at almost any prize-fight on radio or television, it is long past time for those who respect what they cannot create or repair, for the imaginative and for the fastidious, and for those who are alarmed at the continued debasement of human life and values to cry out upon a disgusting outrage against human dignity and decency that has killed some and reduced many to a state bordering upon idiocy

Chest Clinic,
Folkestone, Kent

B G EDELSTON

ANTIBODY-ANTIGEN REACTIONS OBSERVED BY FLUORESCENCE

SIR,—Your annotation of May 31 gives the impression that the Coons technique has scarcely been tried in this country. This is far from the truth: the localisation of tissue antigens in the kidney[1] and the relation between autoantibodies and Hashimoto's disease[2] are but two of the recent studies using the method. Your hope that "simpler techniques will no doubt be introduced" ignores the important contribution recently published in your own columns.[3] This is carrying modesty a bit far.

Department of Bacteriology,
University of Aberdeen.
A. MACDONALD

SIR,—Your annotation reviews a very limited amount of the information which has been obtained by this technique. Studies of viruses, plasma-proteins, and tissue antigens and of antibody production have each produced more papers during the present decade than the study of bacteria or their products. Even in the field you select for detailed review, several contributions have been overlooked.[4-8] It is regrettable, too, that reference to British work is so scanty. The technique has been used in at least nine laboratories and papers from at least six of these have appeared during the last year[9-16]; Weiler's work, also, was done and published in this country.[17] The modification described by Chadwick et al.[14] has simplified the technique, introduced a reliable alternative fluorochrome, and reduced the incidence of non-specific staining. Kaplan[18] has recently described a further modification which eliminates non-specific staining with fluorescein-labelled sera.

Department of Pathology,
Royal Infirmary,
Glasgow
BRUCE CRUICKSHANK

THE RUSSIAN VACCINE

SIR,—The letter of Dr. Liversedge last week was a very fair summary of the position that arises from the publicity given to the Russian vaccine for multiple sclerosis. During the recent visit of the Socialist Medical Association delegation to the Soviet Union, we endeavoured to get some information about this vaccine. Unfortunately we were not able to get in touch with Professor Shubladze, but we had a long conversation with Dr. Zhdanov, a deputy Minister of Health and himself a virologist. We did not gather from him that the vaccine is being widely used in the Soviet Union, and indeed we have been much surprised to find how much of it appears to have been made available for export. He told us that they were very well aware of what had been said about the vaccine in other countries and implied that it had been put back on an experimental basis and was now the subject of further extensive laboratory investigation. This is something, he concluded, which clearly needs testing, and when the results are available they will be published in the scientific press at once.

In these circumstances we have been answering the many queries we have had in a very cautious way and have advised doctors and patients not to be optimistic about it and not to spend large amounts of money on it until more information is available. We agree, however, with Dr. Liversedge that the attitude taken by the Ministry of Health on this is far too negative a one and if the material is to be imported it should be the subject of real scientific test and report.

Kingston Hospital
Pathological Laboratory,
Kingston-upon-Thames, Surrey
D. STARK MURRAY

ZIRCONIUM GRANULOMAS

SIR,—Your annotation (May 31), in reviewing the admirable work of Shelley and Hurley on zirconium granulomas, supported their claim to be the first to demonstrate a granulomatous reaction in the skin by experimental means. In so doing you overlooked the work on beryllium that has been carried out in this country. In 1955 I reported the production of a sarcoid-like granuloma after a positive epidermal reaction to a very dilute solution of beryllium sulphate in a case of beryllium disease.[1] This observation has been confirmed in a second case of my own reported recently,[2] and by Jordan and Darke.[3]

In all these cases the epithelioid reaction has followed the application of very dilute solutions to the skin so that no question of a foreign-body reaction can be entertained. It would appear to be a type of delayed allergic response to minute amounts of beryllium, very comparable with the reaction to zirconium.

Sheffield.
I. B. SNEDDON

STOKES-ADAMS ATTACKS TREATED WITH CORTICOTROPHIN

SIR,—The paper by Dr. Litchfield and his colleagues in your issue of May 3 prompts us to record the following case.

A man aged 68 was admitted to this hospital on April 26 with a history of syncopal attacks for six months. Immediately before admission they were occurring, on average, four or five times daily. An attack was observed shortly after admission. There was the classical pallor, followed by flushing on recovery, of Stokes-Adams syncope. Although, on that occasion, actual cardiac standstill was not confirmed by his pulse or by auscultation, this has been observed in subsequent episodes. The only significant findings were moderate cardiomegaly, free aortic reflux, and a blood-pressure of 200/65 mm. Hg. The electrocardiogram showed a P-R interval of 0·24 seconds and a right bundle-branch block. There was no aortic calcification and the Wassermann reaction was negative.

On the first few hospital days he averaged four to five attacks daily with, however, a number of minor episodes of transient faintness without loss of consciousness. Ephedrine (gr. ½ q.d.s.) and 'Hyperduric' adrenaline (2 ml.) 12-hourly had no effect on the frequency of attacks, so, stimulated by the experiences of Dr. Litchfield and his colleagues, we stopped other drugs on May 6 and substituted prednisilone 20 mg. q.d.s. On May 7 he had forty attacks, the next day three, and he has now remained free for twelve days. His last cardiogram shows a normal P-R interval (0·2 sec.). The right bundle-branch block is unchanged. We are now gradually reducing the steroid.

It is, as Litchfield et al. point out, a matter of common experience that Stokes-Adams attacks vary in frequency

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1. Hill, A. G. S., Cruickshank, B. *Brit. J. exp. Path.* 1953, 34, 27.
2. White, R. G. *Proc. R. Soc. Med.* 1957, 50, 953.
3. Chadwick, C. S., McEntegart, M. G., Nairn, R. C. *Lancet*, 1958, i, 412.
4. Hill, A. G. S., Deane, H. W., Coons, A. H. *J. exp. Med.* 1950, 92, 35.
5. Schmidt, W. C. *ibid*, 1952, 95, 105.
6. Sheldon, W. H. *Proc. Soc. exp. Biol., N.Y.* 1953, 84, 165.
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8. Poetschke, G., Killisch, L., Uehleke, H. *Z. Immun.-Forsch.* 1957, 114, 406.
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12. Sharp, A. A., Bidwell, E. *Lancet*, 1957, ii, 359.
13. White, R. G. *Proc. R. Soc. Med.* 1957, 50, 953.
14. Chadwick, C. S., McEntegart, M. G., Nairn, R. C. *Lancet*, 1958, i, 412.
15. Cruickshank, B., Currie, A. R. *Immunology*, 1958, 1, 13.
16. McEntegart, M. G., Chadwick, C. S., Nairn, R. C. *Brit. J. vener. Dis.* 1958, 34, 1.
17. Weiler, E. *Brit. J. Cancer*, 1956, 10, 560.
18. Kaplan, M. H. *J. Immunol.* 1958, 80, 254.

1. Sneddon, I. B. *Brit. med. J.* 1955, i, 1448.
2. Sneddon, I. B. *Postgrad. med. J.* 1958, 34, 262.
3. Jordan, J. W., Darke, C. S. *Thorax*, 1958, 13, 69.

in an unpredictable manner without any specific treatment We feel, however, that this patient's clinical course justifies this interim letter, and we await with interest both future developments in our patient and the experience of others in similar circumstances

Prospect Park Hospital,
Reading

M J TEMPLER
WAVERLEY

THE TOURNIQUET

SIR,—Your leader of May 31 put the case for and against the tourniquet with clarity and balanced judgment, but I think does not answer effectively two points I made in my letter of March 15 infection is likely to establish itself more easily, and damaging effects can follow the sometimes very great œdema

Your erudite leader says there is no clear evidence on the increased liability to infection But the case for this is self-evident Whilst the tourniquet is on, the life processes of the cells, the reaction to infection, the responses to trauma are in abeyance It is on to these defenceless cells that staphylococci fall, a perfect culture medium And we must remember that they divide every half hour But when the constrictor is removed conditions still remain favourable, for the inability of the lymphatics to absorb the œdema, which may be very great and last for days, denotes severe damage to the mechanism of absorption, the permeability of the endothelium of the lymphatics and the ability of the muscles to assist mechanically Thus not only is there stagnant plasma in the tissue-spaces but also no fresh plasma containing immune bodies can exude into them The conditions are ideal for infection There is no need of experiments to prove this contention, for the facts stand out and only observation and a little thought are needed to recognise the situation

Paralysis of the hand and infection in a limb are serious risks and I doubt if these limbs are ever restored completely to normal It is small consolation to a patient suffering paralysis or a long drawn-out infection to be told that his predicament is rare and only exceptionally permanent when he knows that it could have been avoided altogether had the surgeon adopted another method of operating

Basingstoke

CHARLES A PANNETT

DISPLAYING AXILLARY LYMPHATICS

SIR,—Mr Heanley asks (May 31, p 1181) whether anyone has published data on axillary lymphatics using patent-blue dye to visualise them He will find references to it in a Hunterian lecture [1] and in other papers on the lymphatic system by Mr G W Taylor and myself describing work done at St Bartholomew's and St Thomas's Hospitals during the past decade

We found, like Mr Heanley, that the lymphatic pathways from the arm could be readily identified in the axilla during the operation of radical mastectomy It appeared to us that preservation of the lymphatic pathways from the arm was incompatible with the clearance of the axilla which is part of Halsted's radical mastectomy, because they were so intermingled with the pathways draining the breast Mr R S Murley also studied some of his patients in the same way and came to the same conclusion We have not pursued the problem further, because we abandoned the radical operation for other reasons some years ago It may well be that Mr Heanley may find by careful dissection that the two pathways can be separated and it will be interesting to hear of his results in the future

St Thomas's Hospital Medical School,
London, S E 1

J B KINMONTH

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[1] *Ann R Coll Surg Engl* 1954, 15, 300, *Ann Surg* 1954, 139, 129

TREATMENT OF OBESITY

SIR,—Dr Jacoby (*May 31*) suggests that weight reduction by conventional methods, or by the hydrophilic-colloid method, is not enduring In the case of the colloid method my experience is that after six to eight weeks' treatment the patient has become "reconditioned" to eating sensibly and continues on the right path for a variable period thereafter This may vary from weeks or months to an indefinite period, and in any case if the patient's dietetic habits relapse this can be easily remedied by another course of treatment, which is inexpensive, non-toxic, and needs the minimum of the doctor's time

In the criteria I suggested for weight-reducing treatments (April 26) I omitted to include "economy of doctor's time" This is most desirable, but I note Dr Jacoby recommends psychotherapy as an alternative—and though I agree that psychological factors exist in some cases, the obese are many and the psychiatrists few For this reason psychotherapy seems impractical for the masses, quite apart from the fact that the professional-time factor would make the cost very high

I am grateful to another physician who, in a personal communication, pointed out that, ætiologically, it is not so much overeating as incorrect selection of food which is important Of course he is right, "incorrect eating" is a much more apt term than "overeating" In giving instructions to patients who are about to reduce I *do not* give a *definite* diet, because of the efficacy of the method, this is unnecessary, but the patient receives a written explanation of the principles of correct food selection My correspondent relied on re-educating his patients to better dietary habits, but I feel that without some effective aid to bring about the "reconditioning" it must be hard going for the doctor and hard on the patient

Harperbury Hospital,
near St Albans

JOHN N BADHAM

SIR,—Dr Jacoby (May 31) appears to have misunderstood my letter of April 5, for he accuses me of extolling the very type of treatment that my letter criticised

"It is easy", he states, "to put a patient on a diet, give appetite-reducing pills, and get considerable reduction in weight" This seems doubtful A recent examination of the records of 150 patients (average overweight 56 lb) treated for obesity along these lines showed that only 8 of them reached normal weight

"This weight is regained almost invariably once supervision is discontinued" This is borne out by work done both here and elsewhere 114 patients treated for severe obesity with satisfactory weight loss one to eight years previously were recalled to hospital Their average weight was only 1 lb less than before treatment began Only 3 had reached normal weight

Because of the poor results of previous treatment, an obesity clinic was started in this hospital The therapeutic regimen is very different from that which Dr Jacoby implies we are using He states that my letter "completely ignores the psychosomatic aspects of obesity" Yet the letter said, "time has been spent in discovering the background of each patient's obesity and the special difficulties in treating it"

The patients attend the clinic frequently (usually at intervals of two or four weeks for the first months) and see the *same* doctor at each visit All but a small proportion have had previous medical treatment which failed Yet most of them find that the personal interest taken in them and the opportunity to discuss their problems enables them to reach normal weight, often without the use of drugs 105 patients have attended regularly until discharge over the past two years 102 of them reached normal weight These have all been followed up, and none has so far relapsed

The psychological background of obesity, described by Dr Jacoby, has been known for many years In some patients it is obvious In many it is undetectable, either by patient or doctor, the fact that these patients reach and maintain normal weight without difficulty suggests that even if "unsatisfied oral needs" are the cause of the obesity, they can for practical purposes, be regarded as "within normal limits".

Stressed less often than the psychological causes of obesity are the psychological results of the condition. The improvement in outlook and mental state of many patients after losing several stones in weight is enormous. They are able to cope with their lives and their problems much more effectively than before. The improvement in health and appearance helps them to do this, and adds to their determination "never to let it happen again".

But before this stage is reached, a patient may pass through a period of difficulty, with multiple psychosomatic symptoms. Many state that these symptoms were the cause of failure of previous treatments. It is during this period that attendance at the clinic is particularly valuable. Often discussion and reassurance is all that is required, and treatment continues smoothly.

"Obese patients require psychotherapy," writes Dr Jacoby. Experience in this clinic suggests that the majority require no more than is achieved by repeated conversations with a doctor who is interested in them. But that much they do need.

I thank Dr Alexander Kahan, consultant physician at St. James' Hospital, Balham, for permission to do this work and for his frequent advice, helpful criticism, and constant encouragement. I thank him also for permission to publish this letter.

Obesity Clinic,
St. James' Hospital,
Balham, S.W.12.

A. G. MULLINS

INFLUENCE OF THE TEMPERATURE OF INGESTED SUGAR SOLUTIONS ON THE BLOOD-SUGAR LEVEL

SIR,—Bicknell[1] described a rarely mentioned and interesting difference between the action of cold and warm foods. After eating cold foods hypoglycæmia develops sooner than after the ingestion of warm foods. In those diabetic patients who got their insulin before a supper consisting of cold meat, hypoglycæmia developed sooner than in patients whose supper consisted of warm meat of the same quality and quantity.

The inner temperature of the stomach can be changed significantly by the temperature of the ingested food.[2] The activity of intestinal absorption increases in proportion to the temperature of the ingested food between 20° and 40° C.[3] Some findings suggest that cold foods leave the stomach more rapidly and peristalsis increases—that is, absorption is less efficient. On the other hand, some observations on the stomach emptying time for cold foods compared with foods of normal temperature indicate that cold food may in fact leave the stomach more slowly.[4]

The published data are thus conflicting and the further examination of the problem might be important, for changes in blood-sugar level, and the eventual change in the blood level of other nutriments, can have a decisive influence on the function of the endocrine system and so upon the whole organism.

We therefore decided to examine the difference between the effect of warm and cold foods upon the blood-sugar level in animal experiments.

12 male albino rats, fasting for twenty-four hours, received 3 g. of glucose in 6 ml. of water into the stomach through a gastric tube. The animals were paired, one receiving the solution at a temperature of 2–6° C, the other at 38–42° C. Blood samples were taken from the rats' tails before passing the gastric tube, and then every thirty minutes for two hours. At the end of the experiment the rats were sacrificed by decapitation. The intestinal tract was washed out with isotonic NaCl solution, and the sugar content of the washing fluid was determined by the Hagedorn-Jensen method.

After the ingestion of cold glucose solution the blood-sugar curve was low and drawn out, after a warm solution the curve rose steeply. The glucose content of the intestinal fluid was significantly higher in those animals who got the cold solution—that is, absorption was faster in the warm group.

The blood-sugar rise was about 68% greater after the administration of warm glucose solution than after ingestion of cold glucose solution.

This phenomenon is of importance in the dietetic treatment of diabetic patients. The consumption of a cold cream rich in sugar and protein causes a uniform and slow rise of the blood-sugar level, and this effect might be enhanced by the action of proteins in decreasing the blood-sugar.[5]

The published data and our own findings suggest that this matter needs further consideration.

First Department of Pediatrics,
Medical University, Budapest.
Institute of Nutrition, Budapest.

L. BARTA
M. BEDO

TOXÆMIA IN PREGNANCY

SIR,—I read with interest and with some astonishment your account (June 7, p. 1235) of a new film on this subject which was introduced at its first showing by Professor R. J. Kellar. You describe it in the following words:

> "Skilfully photographed in colour, it points good-humouredly to the dos and don'ts relevant to toxæmia. Mrs Stout, caught during a light snack at the fish-and-chip shop, Mrs Pale, a heavy smoker and inadequate eater, and Mrs Weary, struggling for prodigious hours a day on behalf of her large family, illustrate the don'ts. The advice about diet includes the instruction to use salt in cooking but not otherwise. The tone of the film seems exactly right for its purpose, and several obstetricians who saw it last week said how much they admired it."

I am interested in toxæmia of pregnancy and would like to have references to the evidence that it is commoner in stout women. If this is true, it would seem likely that Mrs Pale, although saving up for carcinoma of the bronchus in later life, was probably protecting herself from toxæmia, or is there also evidence that it is particularly common in thin women? If so I would again like the reference. Perhaps Mrs Pale's diet was only inadequate in iron and vitamins, but I know no evidence that such inadequacy predisposes to toxæmia, and my recent survey of the incidence of toxæmia in the wives of young doctors would not lead one to suppose that it was a factor.

Finally, Mrs Weary is obviously meant to depict the unfortunate woman whose child-income ratio is too high. Does the film make it clear that she has already had toxæmia with her other pregnancies? If not she is surely the most unlikely person to develop it, for one of the few facts fully established about this mysterious condition is that it is much more common in first pregnancies and very rarely occurs for the first time in a third or fourth or subsequent pregnancy. If there is substance in my criticisms would it not have been better if the obstetricians who saw it had condemned rather than admired a film which departed so far from scientific truth?

Department of Medicine,
The Royal Infirmary,
Manchester.

ROBERT PLATT

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1 Bicknell, F. *Lancet*, 1957, i, 389.
2 Glatzel, H. Krankenernährung. Berlin, 1953.
3 Höber, R. Physikalische Chemie der Zellen und Gewebe. Berne, 1947.
4 Portis, S. A. Diseases of the Digestive System. London, 1953.
5 S[illegible], M. *Lancet*, 1957, i, 317.

ÆTIOLOGY OF PRE-ECLAMPTIC TOXÆMIA

SIR,—Professor Gray and Dr Rinsler in their letter of April 12 claim to have demolished the foundations of the long and widely held belief that the adrenal cortex plays a major role in the ætiology of pre-eclamptic toxæmia and eclampsia With respect I submit that their claim cannot be substantiated Nowhere in my paper of Jan 18 did I suggest that the glucocorticoids were responsible for the pre-eclamptic syndrome On the contrary, I expressly stated that the mineralocorticoids were "probably the hormones chiefly involved in pregnancy toxæmia" I also gave reasons for believing that aldosterone was not the responsible mineralocorticoid I now suggest that it may be deoxycortone acetate or a compound with similar action

It would, indeed, be rash to base an opinion regarding the secretory activity of the adrenal cortex on histological appearances alone, for they are notoriously difficult to interpret There is, however, another possible source of active hormones—namely, the placenta—which is known to contain substances that possess adrenocortical-like activity, though the yield of bioactivity is much less than that from adrenal tissue It is not yet known whether the active factors have been produced in the placenta or simply stored there after having been transported from some extraplacental source, [1] though there are certain facts that favour the adrenal as the main site of their production As to potassium excretion, which is usually increased in adrenal cortical hyperactivity, it is well known that there are circumstances in which it is not, and until more is known about it, it would be wise to refrain from basing important conclusions upon it

I thank all the correspondents who have contributed to the discussion on my paper I do not wish to support any particular theory or point or view on this difficult problem merely because it is my own, but only to arrive at the truth

Sydney F J BROWNE

SURGERY OF PARKINSONISM

SIR,—I have read Mr Oliver's communication (May 24, p 1121) describing the surgical techniques used in the treatment of Parkinson's syndrome and would offer the following comments

Whereas the postmortem lesions present in non-infective parkinsonism are well understood, the precise ætiology remains entirely unknown Surgical procedures are purely empirical and are not based on any sound physiological theory Furthermore, if some improvement in the rigidity is achieved by the various operations described, relapse is certain as the lesions in the midbrain progress

I have recently discussed with eminent American authorities the minimum indications which must be present before surgery or irradiation by multibeam ultrasonic waves is considered, and we agreed they are

(1) Unilateral rigidity and tremor, preferably in one limb only

(2) Absence of other serious disease (this means that the patients must be a good operative risk below the age of 50)

(3) Failure of drug therapy

I have recently studied in great detail the case-histories of 398 patients attending my Parkinson's clinic regularly, and only 15 were found to have these characteristics and all have responded satisfactorily to B-dimethylaminoethyl-2-methylbenzhydryl hydrochloride ('Disipal'), ethopropazine hydrochloride ('Lysivane'), 10-(1-methyl-3-piperidylmethyl)-phenothiazine (pecazine) ('Pacatal'), or benzhexol hydrochloride ('Artane'), or a combination of these drugs 3 patients suffering from unilateral tremor and rigidity were subject to pallidectomy before attending my clinic, and after the operation the disease rapidly spread to both sides It is concluded that surgery offers little hope of relief for those suffering from parkinsonism

Dudley Road Hospital,
Birmingham R O GILLHESPY

VISITING MENTAL HOSPITALS

SIR,—I have read Mr Woodley's letters of May 17 and June 7 with amazement, for I believe that medical superintendents in general welcome visitors to their mental hospitals

Here we are fortunate in that we have a very active League of Friends, who make a special feature of visiting lonely patients, and as all the wards are open they come in and go out at any convenient time as they please If Mr Woodley and his party care to visit us I shall be pleased to give them the same facilities

The Central Hospital,
nr Warwick E S STERN

RETINAL PHOTOGRAPHY

Mr A H DEGENHARDT, F B O A, a director of Degenhardt and Co Ltd, Carl Zeiss agents, writes

"Your editorial on retinal photography in the issue of May 10 says 'In this respect modern retinal cameras are less satisfactory than the original Zeiss-Nordenson camera, for with them the photograph records a smaller area of fundus and consequently ' This may be true of some modern retinal cameras but it is a criticism which certainly may not be levelled against the new Zeiss instrument In this the field of view is considerably larger than in the old Nordenson and as the magnification is less it follows that the area of fundus recorded is appreciably larger than in the earlier instrument"

Public Health

Poliomyelitis Vaccination

WITH the arrival of a further 1,000,000 doses of Canadian Salk vaccine, the initial order of 4,000,000 doses placed with the Connaught Laboratories, Toronto, last September, has been completed This final consignment was not expected until later this month, but the laboratories hastened delivery to help the current British vaccination programme All the Canadian Salk vaccine has passed the M R C tests This latest consignment brings the total of vaccine, both British type and Salk, which has been distributed throughout Great Britain, to just over $13^1/_2$ million doses, of which $9^1/_2$ million have been distributed since last January

Registration returns from the local authorities show that by April 30 just over 6,250,000 children and other priority groups had registered, of whom just over 3,640,000 had received both injections, or were awaiting their second The present position is that with the latest Canadian batch enough vaccine will have been distributed to cover all those registered and awaiting vaccination on April 30, but some allowance must be made for unavoidable wastage A statement from the Ministry of Health says "as far as we can judge" there should now be enough vaccine to cover practically all of those in the priority groups who had registered by April 30 Registrations are, of course, continuing and vaccination will also go on during the summer months Further batches of vaccine, mostly Salk, will continue to be issued to keep pace with new registrations"

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[1] Johnson, R. H, Haines, W J *Science*, 1952, 116, 456

Food-poisoning in Birmingham

EIGHTEEN employees at the Birmingham works of a biscuit manufacturer were taken to hospital with food-poisoning on June 6 They fell ill a few hours after a lunch of sausage-and-onion pie at the works canteen Six patients were detained in hospital for observation, but it is reported [1] that none of them is seriously ill Further inquiries into the cause of the outbreak are proceeding

X-ray Machines in Shoe Shops

REQUIREMENTS for the control of shoe-fitting fluoroscopes have been formulated by the Home Office and have been accepted on behalf of the manufacturers and users by the Pedoscope Co , Ltd , the Footwear Distributors Federation, and the Retail Distributors Association They include

(1) The dose-rate in the beam of the machine about the position occupied by the sole of the foot when the machine is in use shall not exceed 8 r per minute, and the dose-rate on the outer surface of the machine shall be such that the dose received by the fitter shall not exceed 0·03 r per week.

(2) The machine shall be fitted with a three-selector device labelled for men women, and children, and the exposure conditions shall be such that the dose-rate when the control for women is operated shall not exceed 6 r per minute, and when the control for children is operated, 4 8 r per minute

(3) The machine shall be fitted with a time-limiting device so that the X-ray beam cannot be switched on for more than 5 seconds at a time and each exposure is followed by a dead time of not less than 30 seconds before the tube can be re-excited

(4) The manufacturers shall not, after July 1, 1958, supply any machine that does not conform with these requirements, and they shall, as soon as practicable and in any event before July 1, 1963, provide for the alteration of any existing machines which the users are willing to have altered so that they comply with the requirements

(5) In each shop using a shoe-fitting fluoroscope there shall be at least one member of the staff on duty who understands the appropriate control measures to be exercised

(6) The machine shall wherever practicable be situated close to and facing a wall with the foot-aperture directed away from the normal traffic of customers and staff

(7) A notice shall be mounted on each machine near the view-screen so that it can easily be read by customers in the following terms '*Notice* —Repeated exposure to X rays may be harmful It is unwise for customers to have more than twelve shoe-fitting exposures a year", and before carrying out an X-ray examination the fitter shall draw the client s attention to the notice displayed

(8) Users of a machine supplied before July 1, 1958, shall not use it after July 1, 1963, unless it conformed with requirements 1 to 3 above at the time of delivery or is subsequently altered to conform.

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[1] *Birmingham Post*, June 7

Infectious Diseases in England and Wales

Disease	Week ended May				
	3	10	17	24	31*
Diphtheria	3	4	1	[illegible]	3
Dysentery	816	771	803	1084	781
Encephalitis					
Infective	5	6	2	2	6
Post-infectious	3	6	1	4	2
Food poisoning	176	159	197	177	138
Measles excluding rubella	3699	3572	4559	5258	5527
Meningococcal infection	24	16	17	25	19
Ophthalmia neonatorum	23	23	27	25	17
Paratyphoid fever	2	7	7	3	1
Pneumonia primary or influenzal	425	30[illegible]	243	255	238
Poliomyelitis					
Paralytic	11	13	12	21	22
Non paralytic	9	7	4	7	5
Puerperal pyrexia	200	220	179	223	200
Scarlet fever	756	706	749	746	653
Smallpox	—	1	—	2	—
Tuberculosis					
Respiratory	646	565	659	581	530
Meninges and C.N S	10	10	4	8	6
Other	79	57	79	81	46
Typhoid fever	5	4	2	4	5
Whooping-cough	678	652	605	612	558

* Not including late returns.

Obituary

JAMES THOMPSON DUNCAN

F.R.C S I , D T.M. & H.

Dr J T Duncan, who died on June 3, was the first reader in medical mycology in the University of London He held this post at the London School of Hygiene and Tropical Medicine, where he was director of the standard mycological laboratory of this country

Before he began to study medicine he was a chartered accountant for five years, and he qualified from the Royal College of Surgeons in Ireland in 1911 After holding house-appointments at the Adelaide Hospital in Dublin he joined the staff of the King Edward VII College of Medicine in Singapore, and he also held the part-time appointment of Government pathologist in the Straits Settlements In 1916 he was appointed lecturer in clinical medicine and pathology at the college, and for two years he was also acting principal. In 1919 he returned to this country, and the following year he became lecturer in pathology at the London School of Tropical Medicine When the London School of Hygiene was established in 1927 he was appointed lecturer in the department of bacteriology and Milner fellow

Duncan had early become interested in the fungus diseases, and when the Medical Research Council's committee on medical mycology, of which he was chairman, decided during the 1939–45 war to survey the fungus diseases of Great Britain he was put in charge of the investigation Requests for material brought about 1500 specimens, and Duncan was largely responsible for their examination and identification This work was at first carried out at Winchester, where he was in charge of the war-time emergency public health laboratory, and was continued at the London School of Hygiene and Tropical Medicine after his return to his academic duties At this time he was also collaborating with Dr S P Wiltshire and Dr Charles Willcocks in editing the *Annotated Bibliography of Medical Mycology*, which was published in 1947 In that year Duncan's contribution to medical mycology was officially recognised when the University of London created a readership for him

P M -B , who has been his friend for nearly forty years, writes

Duncan was a very popular person with his modest ways, soft-spoken Irish brogue, and cheerful friendly disposition. He possessed the true and devoted scientific spirit and worked away, often with a smile and a jest, at many branches of pathology and bacteriology Although he was a good critic he was quite free from any thoughts of jealousy, hatred, malice, or uncharitableness His own work was of fundamental and lasting value. He brought order out of chaos and regularised the nomenclature of the pathogenic fungi of man. Only those familiar with this subject can realise what he did to put mycology on the map For some years he had been writing a standard book on medical mycology to which he had given all his energies and thought. It was near completion when he died, and it is to be hoped that it will soon see the light of day

Duncan was fortunate in having, as his pupil and assistant, his daughter Mrs Jacqueline Walker, who is director and lecturer in her father's old department.

JOHN FRANCIS COATES

M D Brist , M.R.C.P

Dr John Coates, consulting pædiatrician to the South Somerset clinical area, died at Bridgwater on May 24 at the age of 50

His father is Dr Richard Coates, of Burnham-on-Sea After graduating M.B with honours from the University of

Bristol in 1930, John Coates held house-appointments at Bristol General Hospital In 1935 he took the M R C P and his M D with distinction Soon afterwards he returned to Bridgwater to take over the family practice on his father's retirement Later he became honorary medical officer to Bridgwater General Hospital

During the late war he served with the R A M C He spent most of his time in the Middle East, and, with the rank of lieut -colonel, was medical adviser to the Persia and Iraq Commands After he returned to civilian life he decided to specialise in pædiatrics, and held an appointment as senior resident medical officer at the Victoria Hospital for Children in Chelsea before returning to Somerset Soon afterwards he was appointed to the staffs of Musgrove Park Hospital and Yeovil Hospital

H P writes

I first met John Coates nearly thirty years ago when we were members of the " house " at the Bristol General Hospital Already he was acquiring the great learning that marked him out He was reading deeply in the underlying philosophy of medicine at an academic standard outside the range of other housemen He was determined to lay firm foundations of a wide mastery of medicine, and to this end spent several years as a resident in general medicine and surgery and in the special departments None the less, then as through all his life, he kept the " common touch ", and was a delightful and cheery companion His room was a meeting-place where shop chatter *mixed with music, both lowbrow and classical*

After the war he specialised as a pædiatrician, and his name rapidly became identified with this specialty from Yeovil to Minehead and from Glastonbury to Taunton His centre and pride were his pædiatric wards at the Taunton and Somerset Hospital, but he was called to all the hospitals around He paid for his success in having little time to call his own It was a ready saying at social parties that if the 'phone went it was sure to be for " Jackie " His colleagues entrusted him with the postgraduate studies of their area, and the weekend courses he organised were a pleasure to both attending practitioners and lecturers He will be missed for his wise medical counsel, his care of the illnesses of the children of his colleagues, and the friendship and hospitality he and his wife provided for their many friends

Appointments

Carr, G R, CH M Manc, M D Michigan, F R C S consultant surgeon, Stockport and Buxton group of hospitals

Chadwick, D L, M D Manc, F R C S, D L O part-time consultant E N T surgeon, Crumpsall, Ancoats, and Manchester Ear Hospitals

Clynick, F E, M B, B SC St And, F F A R.C S, D A part-time consultant anæsthetist, St Peter's, St Paul s, and St Philip s Hospitals, London

Kelly, J A, M B N U I school M O, Leeds

Milligan, Maire P, M B, B SC N U I, D P H senior assistant county M O and school M O, Brighouse division, West Riding of Yorkshire

Reynolds, D B, M R C S assistant county M O and school M O, Brighouse division, West Riding of Yorkshire

The Hospital for Sick Children, Great Ormond Street, London

Abrahamson, Jack, M B Cape Town house-surgeon

Brett, June E, M B Cantab, F F A R C.S, D A jun

registrar

Barltrop, Donald, M B Lond house-physician

Hatcher, G W, M B Lond, D OBST house-physicia

Ingram, R M, B.M Oxon senior registrar, ophthalm

Kingsmill-Moore, J M, M B Dubl house-surgeon

Larnder, D A, M B N Z, F R C S senior registrar, dermatology

Mackie, D G, M B Adelaide E N T registrar

Stevenson, C J, M D Lond, M R C P senior registrar, dermatology

East Anglian Regio l Hospital Board

Jaffery, S S A anæsthetic registrar,

East Suffolk

Samaan N A C P E medical

Cambridgeshir on Hospital, Wisbech

Smyth H G, M B in mental deficiency

, Little

Notes and News

WORLD HEALTH ASSEMBLY

At the World Health Assembly, which opened in Minneapolis, Minnesota, on May 30 after a session commemorating the tenth anniversary of the World Health Organisation,[1] Dr Leroy E Burney, surgeon-general of the U S Public Health Service, was elected president Dr Burney declared that W H O 's role should be fourfold (1) to coordinate and help strengthen research through scientific meetings and the dissemination of literature, (2) to aid in training health personnel, (3) to help reduce the lag between the discovery and the application of new methods of diagnosis and treatment, and (4) to enlist the participation of groups outside the traditional health setting—such as occupational, welfare, social, and education workers Dr Burney presented the Leon Bernard Foundation prize to Dr Thomas Parran, now dean of the Graduate School of Public Health in the University of Pennsylvania

In the debate on the Director-General's annual report for 1957 Prof V M Zhdanov (Soviet Union) indicated his delegation's approval of the emphasis on the eradication of communicable diseases such as malaria He added that the Soviet Union, with its vast facilities for the control of communicable diseases, in the form of both institutions and specialised personnel, was ready to accept medical workers from abroad for training and to send its own staff to other countries to help further such campaigns He praised the work of W H O 's influenza centres in dealing with the pandemic of 1957 and the achievements of the W H O Expert Committee on Poliomyelitis The U S S R was ready, he said, to participate in this exchange of scientific information

A budget of $14,300,000 for 1959, proposed by Dr M G Candau, director-general of W H O, was approved unanimously by the two main committees In the past ten years W H O 's income has expanded steadily from $5 million A report by W H O 's external auditor revealed that 97 08% of contributions to the 1957 regular budget had been received from active member States—the highest percentage since the Organisation's inception The Executive Board submitted a proposal to encourage contributions to the World Malaria Fund from all possible sources Dr T W Tewari said that India's malaria-control campaign had now been transformed into an eradication campaign, with 230 anti-malaria teams in the field, India would pay the entire running costs The Assembly elected Tunisia to designate a person to serve for a year on the Executive Board, to complete the three-year term of the member designated by Syria, now that that country has merged with Egypt to form the United Arab Republic At a meeting of the programme and budget committee, several delegates deplored the fact that the high cost of vaccine prevented them from organising extensive poliomyelitis-immunisation programmes

AN INJUSTICE MITIGATED

The rules governing grants to boys and girls who win State scholarships have been grossly unfair to many parents, because of ans test In principle there ought to be no
means tes who pays his required contribution to
the comm form of taxes, should be entitled to
whatever t y offers in the way of educational bene-
fits, and it that the more a parent pays into the
common c he can hope for any help out of it
But, theory has le c patent injustice
in practice test unrealistic
deciding father of olar shall pay,
only for enses borne
relation the his contri-
has y his income
—so d surtax "
professional
too large an

income to qualify for a grant but too small an income to pay for a university education for their son or daughter Few parents, unless they have capital, can now afford to send more than one, or possibly two, children to the university in the absence of any kind of grant, and in families clever enough to have several State scholars the only way in which university education could be secured for all of them has been for the father to retire from work—or from life "I could not have gone to the university if my father had not died", some students have said

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Clynick, F E, M B, B SC St And, F F A R C S, D A part-time consultant anæsthetist, St Peter s, St Paul s, and St Philip s Hospitals, London

Kelly, J A, M B N U I school M O, Leeds

Milligan, Maire P, M B, B SC N U I, D P H senior assistant county M O and school M O, Brighouse division, West Riding of Yorkshire

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Barltrop, Donald, M B Lond house-physician

Hatcher, G W, M B Lond, D OBST house-physician

Ingram, R M, B.M Oxon senior registrar, ophthalmic department.

Kingsmill-Moore, J M, M B Dubl house-surgeon

Larnder, D A, M B N Z, F R C S senior registrar, department of dermatology

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In the debate on the Director-General's annual report for 1957 Prof V M Zhdanov (Soviet Union) indicated his delegation's approval of the emphasis on the eradication of communicable diseases such as malaria He added that the Soviet Union, with its vast facilities for the control of communicable diseases, in the form of both institutions and specialised personnel, was ready to accept medical workers from abroad for training and to send its own staff to other countries to help further such campaigns He praised the work of W H O 's influenza centres in dealing with the pandemic of 1957 and the achievements of the W H O Expert Committee on Poliomyelitis The U S S R was ready, he said, to participate in this exchange of scientific information

A budget of $14,300,000 for 1959, proposed by Dr M G Candau, director-general of W H O, was approved unanimously by the two main committees In the past ten years W H O 's income has expanded steadily from $5 million A report by W H O 's external auditor revealed that 97 08% of contributions to the 1957 regular budget had been received from active member States—the highest percentage since the Organisation's inception The Executive Board submitted a proposal to encourage contributions to the World Malaria Fund from all possible sources Dr T W Tewari said that India's malaria-control campaign had now been transformed into an eradication campaign, with 230 anti-malaria teams in the field, India would pay the entire running costs The Assembly elected Tunisia to designate a person to serve for a year on the Executive Board, to complete the three-year term of the member designated by Syria, now that that country has merged with Egypt to form the United Arab Republic At a meeting of the programme and budget committee, several delegates deplored the fact that the high cost of vaccine prevented them from organising extensive poliomyelitis-immunisation programmes

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The rules governing grants to boys and girls who win State scholarships have been grossly unfair to many parents, because of its means test In principle there ought to be no means test any parent who pays his required contribution to the community, in the form of taxes, should be entitled to whatever the community offers in the way of educational benefits, and it is paradoxical that the more a parent pays into the common chest, the less he can hope for any help out of it But, theory apart, the system has led to quite patent injustice in practice because the means test itself has been unrealistic In deciding how much the father of a State scholar shall pay, not only have the allowances for his other expenses borne little relation to the facts, but the scale for fixing his contribution has become progressively more severe as his income increases—so that he has sometimes paid " a second surtax "

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Dr Russell, who is 39 years of age, graduated in *medicine* at Aberdeen in 1942 From 1943 to 1946 he served with the Royal Air Force medical branch On demobilisation he returned to Aberdeen, and after holding gynæcological and obstetrical house-appointments he became registrar at the Aberdeen Maternity Hospital He took the M R C O G in 1949, and a year later he went to Newcastle as first assistant in obstetrics and gynæcology in the University of Durham He was appointed senior lecturer in the department in 1956, and he is also consultant obstetrician and gynæcologist to the United Newcastle Hospitals He was elected F R.C.O G last month. With colleagues in the departments of child health, pathology, and medicine, he has studied various hazards to the life of the fœtus in late pregnancy and early in the neonatal period

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Dr D V Hubble has been appointed to the chair of pædiatrics in succession to Dr J M Smellie, who retires at the end of September

Dr Hubble qualified from St Bartholomew's Hospital in 1924, and after holding house-appointments there he joined Dr F G Lescher in practice in Derby Soon afterwards he was appointed to the staff of the Derbyshire Royal Infirmary, the Derby City Hospital, and the Derbyshire Children's Hospital He is an examiner in medicine in the University of Sheffield and a member of the medical committee of the Sheffield Regional Hospital Board He is also a member of the council of the Association of Physicians and of the British Pædiatric Association He was elected F R C P in 1954 His published work reflects his interest in metabolism, endocrinology, pædiatrics, and genetics and includes papers on Cushing's syndrome, homœostasis, familial cretinism, the adrenogenital syndrome, and glycogen storage disease of the liver He is also eminent as a Johnsonian and has published studies on Charles Darwin as a practising invalid

Prof R A McCance will deliver the Leonard Parsons lectures in 1959

University of Edinburgh

Mr John Boyes, professor of oral surgery in the University of Durham, has been appointed to the chair of dental surgery in succession to Prof A C W Hutchinson, and is expected to take up his appointment in October

Professor Boyes, who is 45 years of age, was educated at George Watson's College, Edinburgh, the School of Medicine of the Royal Colleges, Edinburgh, and the Edinburgh Dental Hospital and School He took the L D S in 1934 and his medical qualification the following year After holding appointments as school dental officer to Ayr County Council and resident dental house-surgeon at the Middlesex Hospital, London, he joined the staff of the Bangour Hospital, West Lothian, where from 1940 he held the appointment of resident surgical and dental officer to the plastic and jaw injury unit In 1945 he took the F R C S E, and the same year he became first assistant in the department of oral pathology of the Sutherland Dental Hospital, Newcastle upon Tyne He was appointed in 1946 to the Nuffield chair of oral medicine in the University of Durham He is also director of the Newcastle Dental Hospital and dental surgeon to the Royal Victoria Infirmary

Royal College of Surgeons of England

Buckston Browne Dinner—Accommodation at this dinner (tickets £2 10s) is limited and fellows or members who wish to attend should write immediately to Mr W F Davis, deputy secretary of the college, Lincoln's Inn Fields, London, W C 2

Guy's Hospital Medical School, London

On Monday, Aug 11, at 1 P M at the medical school, London Bridge, S E 1, Dr E P Cronkite of the Brookhaven National Laboratory will speak on some effects of ionising radiation on human beings

International Congress of Angiology

This congress will be held in San Remo, instead of in Venice as formerly announced, from Sept 24 to 28 Further information may be had from the secretariat of the congress, dermatological clinic, University of Pisa, Italy

Beit Fellowships for Medical Research

Prof G F Marrian has been elected a member of the advisory board in place of Dr C H Andrewes, who retires after fourteen years' membership

The following elections to junior fellowships (£900 a year) have been made

Phoebe M Cotes, M B, PH D Lond (at the medical unit, University College Hospital Medical School, London), J G Nicholls, M B, PH D Lond (at the department of physiology, University College, London), G M A Gray, PH D Lond (at the department of biochemistry, Lister Institute of Preventive Medicine, London), J B Gurdon, B A Oxon (at the department of zoology and comparative anatomy, University of Oxford), Margarethe M A Holzbauer, M D Graz, PH.D Edin (at the department of pharmacology, University of Edinburgh), F H Taylor, PH D Lond (at the physical chemical laboratories, department of chemistry, Imperial College, London)

Bristol in 1930, John Coates held house-appointments at Bristol General Hospital In 1935 he took the M R C P and his M D with distinction Soon afterwards he returned to Bridgwater to take over the family practice on his father's retirement Later he became honorary medical officer to Bridgwater General Hospital

During the late war he served with the R A M C He spent most of his time in the Middle East, and, with the rank of lieut -colonel, was medical adviser to the Persia and Iraq Commands After he returned to civilian life he decided to specialise in pædiatrics, and held an appointment as senior resident medical officer at the Victoria Hospital for Children in Chelsea before returning to Somerset Soon afterwards he was appointed to the staffs of Musgrove Park Hospital and Yeovil Hospital

H P writes

I first met John Coates nearly thirty years ago when we were members of the " house " at the Bristol General Hospital Already he was acquiring the great learning that marked him out He was reading deeply in the underlying philosophy of medicine at an academic standard outside the range of other housemen He was determined to lay firm foundations of a wide mastery of medicine, and to this end spent several years as a resident in general medicine and surgery and in the special departments None the less, then as through all his life, he kept the " common touch ", and was a delightful and cheery companion His room was a meeting-place where shop chatter mixed with music, both lowbrow and classical

After the war he specialised as a pædiatrician, and his name rapidly became identified with this specialty from Yeovil to Minehead and from Glastonbury to Taunton His centre and pride were his pædiatric wards at the Taunton and Somerset Hospital, but he was called to all the hospitals around He paid for his success in having little time to call his own It was a ready saying at social parties that if the 'phone went it was sure to be for " Jackie " His colleagues entrusted him with the postgraduate studies of their area, and the weekend courses he organised were a pleasure to both attending practitioners and lecturers He will be missed for his wise medical counsel, his care of the illnesses of the children of his colleagues, and the friendship and hospitality he and his wife provided for their many friends

Appointments

CARR, G R, CH M Manc, M D Michigan, F R C S consultant surgeon, Stockport and Buxton group of hospitals

CHADWICK, D L, M D Manc, F R C S, D L O part-time consultant E N T surgeon, Crumpsall, Ancoats, and Manchester Ear Hospitals

CLYNICK, F E, M B, B SC St And, F F A R C S, D A part-time consultant anæsthetist, St Peter's, St Paul's, and St Philip's Hospitals, London

KELLY, J A, M B N U I school M O, Leeds

MILLIGAN, MAIRE P, M B, B SC N U I, D P H senior assistant county M O and school M O, Brighouse division, West Riding of Yorkshire

REYNOLDS, D B, M R C S assistant county M O and school M O, Brighouse division, West Riding of Yorkshire

The Hospital for Sick Children, Great Ormond Street, London

ABRAHAMSON, JACK, M B Cape Town house-surgeon

BRETT, JUNE E, M B Cantab, F F A R C S, D A junior anæsthetic registrar

BARLTROP, DONALD, M B Lond house-physician

HATCHER, G W, M B Lond, D OBST house-physician

INGRAM, R M, B M Oxon senior registrar, ophthalmic department.

KINGSMILL-MOORE, J M, M B Dubl house-surgeon

LARNDER, D A, M B N Z, F R C S senior registrar, department of dermatology

MACKIE, D G, M B Adelaide E N T registrar

STEVENSON, C J, M D Lond, M R C P senior registrar, department of dermatology

East Anglian Regional Hospital Board

JAFFERY, S S A, M B Osmania anæsthetic registrar, Ipswich and East Suffolk Hospital

SAMAAN, N A, M B Alexandria, M R C P E medical registrar, North Cambridgeshire Hospital and Clarkson Hospital, Wisbech

SMYTH, H G, M B Belf senior registrar in mental deficiency and child psychiatry, Little Plumstead group of hospitals

Notes and News

WORLD HEALTH ASSEMBLY

AT the World Health Assembly, which opened in Minneapolis, Minnesota, on May 30 after a session commemorating the tenth anniversary of the World Health Organisation,[1] Dr Leroy E Burney, surgeon-general of the U S Public Health Service, was elected president Dr Burney declared that W H O 's role should be fourfold (1) to coordinate and help strengthen research through scientific meetings and the dissemination of literature, (2) to aid in training health personnel, (3) to help reduce the lag between the discovery and the application of new methods of diagnosis and treatment, and (4) to enlist the participation of groups outside the traditional health setting—such as occupational, welfare, social, and education workers Dr Burney presented the Leon Bernard Foundation prize to Dr Thomas Parran, now dean of the Graduate School of Public Health in the University of Pennsylvania

In the debate on the Director-General's annual report for 1957 Prof V M Zhdanov (Soviet Union) indicated his delegation's approval of the emphasis on the eradication of communicable diseases such as malaria He added that the Soviet Union, with its vast facilities for the control of communicable diseases, in the form of both institutions and specialised personnel, was ready to accept medical workers from abroad for training and to send its own staff to other countries to help further such campaigns He praised the work of W H O 's influenza centres in dealing with the pandemic of 1957 and the achievements of the W H O Expert Committee on Poliomyelitis The U S S R was ready, he said, to participate in this exchange of scientific information

A budget of $14,300,000 for 1959, proposed by Dr M G Candau, director-general of W H O, was approved unanimously by the two main committees In the past ten years W H O 's income has expanded steadily from $5 million A report by W H O 's external auditor revealed that 97 08% of contributions to the 1957 regular budget had been received from active member States—the highest percentage since the Organisation's inception The Executive Board submitted a proposal to encourage contributions to the World Malaria Fund from all possible sources Dr T W Tewari said that India's malaria-control campaign had now been transformed into an eradication campaign, with 230 anti-malaria teams in the field, India would pay the entire running costs The Assembly elected Tunisia to designate a person to serve for a year on the Executive Board, to complete the three-year term of the member designated by Syria, now that that country has merged with Egypt to form the United Arab Republic At a meeting of the programme and budget committee, several delegates deplored the fact that the high cost of vaccine prevented them from organising extensive poliomyelitis-immunisation programmes

AN INJUSTICE MITIGATED

THE rules governing grants to boys and girls who win State scholarships have been grossly unfair to many parents, because of its means test In principle there ought to be no means test any parent who pays his required contribution to the community, in the form of taxes, should be entitled to whatever the community offers in the way of educational benefits, and it is paradoxical that the more a parent pays into the common chest, the less he can hope for any help out of it But, theory apart, the system has led to quite patent injustice in practice because the means test itself has been unrealistic In deciding how much the father of a State scholar shall pay, not only have the allowances for his other expenses borne little relation to the facts, but the scale for fixing his contribution has become progressively more severe as his income increases—so that he has sometimes paid " a second surtax "

Consequently some parents—especially in the professional range of earnings—have found themselves with too large an

come to qualify for a grant but too small an income to pay r a university education for their son or daughter Few parents, less they have capital. can now afford to send more than e, or possibly two, children to the university in the absence any kind of grant; and in families clever enough to have veral State scholars the only way in which university educa- n could be secured for all of them has been for the father retire from work—or from life. "I could not have gone to e university if my father had not died", some students ve said

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[1] See *Lancet*, June 7, 1958, p 1234

The Ministry of Education is now to spend rather less than 2 million a year in raising the grants (to offset the effects of flation) and in making the means test more tolerable. The ly really satisfactory way of operating such a test would be make it depend on the amount of disposable income— e., what is left after paying all obligatory expenses cluding taxes The Ministry's new arrangements do not do is they conveniently forget that payment of taxes is quite n important obligation. Also the basis of the calculation emains merely the annual income—regardless of whether the arent has plenty of capital or none. But unquestionably the ew rules are a step in the direction of fairness, and they hould make it easier for more of the clever children of medical arents to get the same education as their clever coevals om "under-privileged" homes

COST OF CHLOROTHIAZIDE

WE feel we should clarify the matter of the cost of chloro-hiazide mentioned in our recent leader on oral diuretics May 10) We put the basic cost to the N.H.S of 8 g at s 10½d.; but Mr J H. Fingerhut, of Merck, Sharp and Dohme Ltd., manufacturers of chlorothiazide ('Saluric'), wrote n our issue of May 17 (p 1078) to say that this was wrong. the orrect figure, he said, was *7s 6d* for 8 g He did not make it lear, however, that the discrepancy between the two figures was ntirely due to the removal of purchase tax as from April 1 or the purposes of pricing the change became effective on May 1 and a prescription for saluric written on May 10 (the late of our leader) would have carried a net cost price of *7s 7d* per 8 g Thus, we were ten days out of date in the price we gave. But readers should know that the reduction in the price of chlorothiazide was due to the beneficence of the Treasury

The *total* cost to the N.H.S of 8 g. of chlorothiazide is now made up as follows-

Basic cost plus on-cost	9s	5·57d.
Dispensing fee	1s	2d.
Container allowance		1·55d.
Total (to nearest 1d.)	10s	9d.

University of Cambridge

Lord Adrian has been re-elected vice-chancellor for 1958–59

University of Liverpool

On July 4 the honorary degree of M.CH.ORTH. will be conferred on Sir Walter Mercer

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British Medical Association

Entries are invited for the occupational health prize (£50) and the Katherine Bishop Harman prize (£75) for research into the disorders incident to maternity Further particulars may be had from the secretary of the Association, B M A House, London, W C 1

Association of Sea and Air Port Health Authorities of the British Isles

This Association will hold its annual meeting in Edinburgh, on Thursday and Friday, June 19 and 20 The speakers will include Sir Kenneth Cowan and Dr J B Maguire Further particulars may be had from the Medical Officer of Health, Health Department, Civic Centre, Southampton

Nutrition Society

This society will hold a symposium on applied nutrition, at Queen Elizabeth College, Campden Hill Road, London, W 8, on Friday, July 11 The speakers will include Sir Zachary Cope and Dr J J O'Dwyer Further particulars may be had from Miss D F Hollingsworth, c/o Ministry of Agriculture, Fisheries and Food, Great Westminster House, Horseferry Road, S W 1

Association for Radiation Research

This Association, which has grown out of the Radiation Research Visiting Club, has been formed to bring together research workers of different disciplines with a common interest in radiobiology, radiation chemistry, and radiation physics Dr L H Gray has been elected chairman, Dr C L Smith hon treasurer, and Miss T Alper (experimental radiopathology research unit, Hammersmith Hospital, Ducane Road, London, W 12) hon secretary

Margery Fry Memorial Fund

THE Howard League for Penal Reform invites donations to a trust fund which is to be created in memory of Margery Fry, one of whose chief interests was the prevention of crime and the rehabilitation of offenders It is intended that the fund shall be used for such purposes as the financing of scholarships and research and of pioneer projects for the rehabilitation of offenders, and perhaps to help in setting up an institute of criminology One of the signatories of the appeal is Dame Janet Vaughan, and the treasurer is Mr John Cole, 66, Lincoln's Inn Fields, London, W C 2

Convention on Social Security with Yugoslavia

A convention on social security between the United Kingdom and Yugoslavia has been signed The agreement will cover the benefits provided by the schemes of national insurance, industrial injuries insurance, and family allowances in this country and the corresponding benefits in Yugoslavia Medical treatment provided under the Yugoslav scheme of health insurance will be available in Yugoslavia to people insured under the United Kingdom national insurance scheme and to their dependants whether working or on holiday there The convention will come into operation when it has been ratified, and this date will be announced later

Home for Mentally Handicapped Children

THE Scottish Association of Parents of Handicapped Children is a small voluntary body which was formed four and a half years ago in Glasgow It has already set up a small day centre for mentally handicapped children whom the education authority had not accepted for admission to occupational centres It is now opening (*Glasgow Herald*, May 26) at Craigrownie Castle, Cove, Dunbartonshire, a short-stay home for these children The castle was given to the Association as a free gift, but £7000 was needed to convert it, and the Association had only £400 in cash Much of the work of conversion was done by members and their friends, who also raised enough money to enable the home to receive the first children at the of May It is planned for the home to take 25 children, years and under, for periods of up to eight weeks

Dr W M Court Brown has been awarded a David Anderson-Berry prize and medal by the Royal Society of Edinburgh

Sir Vivian Fuchs is to give an illustrated lecture on his journey to the South Pole at the London Coliseum on Sunday, Sept. 28, at 7 30 P M, in aid of the funds of the National Varicose Foundation Some tickets (5*s*, 7*s* 6*d*, 10*s* 6*d*, 15*s*, £1 1*s*, £2 2*s*) are being reserved for doctors and their families Applications, marked "doctor", should be sent with the money to the treasurer of the Foundation, York Road, S W 11

The annual dinner and dance of the Postgraduate Medical School and *Hammersmith Hospital Association will be held at the Park Lane* Hotel at 7 45 P M on Friday, July 4 Tickets may be had from *Dr D* Abelson, department of medicine, Postgraduate Medical School of London, Ducane Road, London, W 12

The summer dinner of the Oxford Graduates' Medical Club will be held in Merton College, Oxford, on Friday, July 4, at 7 30 P M Dr A M Cooke will be in the chair Members may bring medical men or women as guests Tickets (37*s* 6*d*) may be had before June 25 from Dr Ronald Macbeth, department of otolaryngology, Radcliffe Infirmary, Oxford

The Hospitals' Symphony Orchestra is giving a concert at B M A House, London, W C 1, on Wednesday, July 2, at 8 P M Tickets (3*s* 6*d*, 5*s*, 7*s* 6*d*) can be had from Miss M A Whipp, South Western Hospital, Landor Road, S W 9

The British Diabetic Association is holding an exhibition from June 25 to 28, at Central Hall, Westminster, of some of the foods, products, and equipment which are now available to help diabetics with their diet and daily routine The exhibition will be open daily from 11 A M to 9 P M

A booklet on *Nursing for Men* (No 89) has been published in the Central Youth Employment Executive's Choice of Career series Copies may be had from H M Stationery Office (1*s* 6*d*)

The Board of Registration of Medical Auxiliaries has published a new edition (1957-58) of its register of chiropodists Doctors may obtain free copies from the Board, B M A House, Tavistock Square, London, W C 1

A draft British Standard for X-ray envelopes is being circulated for technical comment to industry and others concerned Views on this document should be submitted before June 25 to the British Standards Institution

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Diary of the Week

JUNE 15 TO 21

Monday, 16th

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W 12
4 P M Dr Brian Ackner Attempted Suicide

Tuesday, 17th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W C 2
5 P M Mr A J Helfet Mechanism of the Derangements of the Medial Meniscus of the Knee (Hunterian lecture)
INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Dr A D Porter Light Sensitivity

Wednesday, 18th

POSTGRADUATE MEDICAL SCHOOL
2 P M Dr T M Pollock *Control of Tuberculosis by B C G* Vaccination
INSTITUTE OF DERMATOLOGY
5 30 P M Dr Henry Haber Eosinophilic Granulomata
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P M. Mr J R Belcher Surgery of Carcinoma of the Bronchus

Thursday, 19th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
2 30 P.M *Urology* Dr W F Whitmore (New York) Surgical Treatment of Bladder Tumours
ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE, 26, Portland Place, W 1
7 30 P M Prof A W Woodruff *Medicine in China Today*
POSTGRADUATE MEDICAL SCHOOL
4 P M Prof Clifford Wilson Prognosis in Bright's Disease
CIBA FOUNDATION
5 P M (Royal Institution, 21, Albemarle Street, W 1) Prof F Bourlière (Paris) Comparative Study of Age Changes (Ciba Foundation lecture)
BRITISH ASSOCIATION OF UROLOGICAL SURGEONS HOME AND OVERSEAS, 47, Lincoln's Inn Fields, W C 2
9 30 A M *Opening of three-day meeting*
HYPNOTHERAPY GROUP
8 P M. (1, Wimpole Street W 1) Dr Louis Rose, Dr J A Hadfield Paranormal Healing

Friday, 20th

POSTGRADUATE MEDICAL SCHOOL
10 A.M Mr James Hardman Surgery of Intracranial *Hæmorrhage*
BRITISH INSTITUTE OF RADIOLOGY, 32, Welbeck Street, W 1
2 P M Radiobiology meeting

The Lancet · Saturday 21 June 1958

ENVIRONMENTAL FACTORS IN RESPIRATORY DISEASE *

D D Reid
M D Aberd, Ph D Lond
READER IN EPIDEMIOLOGY AND VITAL STATISTICS,
LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE, LONDON, W C 1

In the study of respiratory disease in its community setting, I have followed Milroy's precepts "that more diligent and continued attention may be paid than has yet been attempted in this country to the study of the accurate *Geography of Diseases*" and that this must be combined with *Chronology*—the exact timing of the appearance, persistence, and aggravation of disease—"so that some record of its varying natural history may be preserved for the benefit of future times"

Respiratory Illness in Offices

Experience in the epidemiology of tuberculosis has taught us the hazards of the widening circle of human contacts which the child meets on leaving the sheltered environment of home and school It seems sensible, therefore, to apply the methods of collaborative inquiry already used in the schoolroom surveys to investigate environment and respiratory disease in offices where so many spend their working life Accordingly Dr Robert Williams and I set up a small pilot inquiry, designed to exploit bacteriological and clinical methods of studying the occurrence and spread of common colds in London offices of the General Post Office (Reid, Williams, and Hirch 1953)

During an epidemic season, histories of all respiratory affections were elicited by regular weekly inquiry from the staffs working in these offices At the same time, samples of the office air were taken by the slit-sampler method The resulting count both of general bacterial air contaminants and of *Strep salivarius*, which is used as an indicator of air pollution by organisms ejected from the mouth, were plotted against the incidence curve of colds among the office staff Observations of outdoor temperature and indoor humidity were made and charted in the same way

The time sequence of events thus observed was clear enough The sudden autumnal fall in outside temperature coincided with a shutting of windows to maintain a stable indoor temperature The *Strep salivarius* count rose in step with a sharp increase in the incidence of colds This in turn coincided with the outbreak of an epidemic of colds in other members of the G P O staff in the rest of London, and it was followed, about two weeks later, by a rise in the notification-rate of acute pneumonia in the the general population of London

The epidemic conundrum is—does the sudden change in climate precipitate an epidemic of colds and their major sequelæ by prompting the shutting of windows and increasing the pollution of the air by organisms from the throats of the occupants so that colds spread more readily from one to another? Or, if we discount the possibility of virus mutation, does the change, perhaps in temperature or humidity, alter host resistance to minimal infections and multiply the frequency of clinically apparent disease? The problem of the epidemic effects of temperature change has been discussed by writers back to Hippocrates, but it has been more recently studied in the present context of London by workers such as Young (1924), Woods (1928), and the Payling Wrights (1945) The Payling Wrights showed very clearly that the weekly mortality-rate from bronchopneumonia in children under 2 years of age was highly correlated with a fall in the temperature two weeks before They inclined to the view that the climatic change upset the epidemic balance more by lowering resistance than by increasing the ease of spread Our recent work supports that proposition

In the family studies, for example, colds were rather more common among the less adequately clad children Again, a seasonal increase in the secondary-attack rates within households, based on clinically obvious infections, was not paralleled by any contemporary increase in the apparent rate of passage of the indicator organisms from person to person Yet some such increase might have been expected to result from an increased rate of transmission of infection In the schools the incidence of colds was lower in classrooms which were usually kept at higher temperatures Although, in offices, the higher *Strep salivarius* content of the air certainly suggested that the *conditions of poorer ventilation in cold weather might* favour aerial transmission of disease, the whole drift of the evidence appears to minimise the importance of this means of spread in the common cold Carefully controlled observations on the immediate past history of those with acute coryza were consistent with the popular belief that being exposed to chilling was significantly related to the onset of clinically obvious infection In short, it seems likely that the sudden climatic change at the approach of winter precipitates apparent disease among the carriers of an infection which then spreads rapidly by close-range droplet spray or intimate contact through a population made susceptible both by the sudden cold and the low endemic level of infection during the summer

Climatic Change and Air Pollution

Whatever its origin, this seasonal wave of minor respiratory infections is but the forerunner of much more serious respiratory illness, which is certainly related in time to the seasonal changes in temperature and other associated aspects of climate When, however, to the more usual changes in climate are added the sudden temperature inversion and humidity of fog, the whole pattern of morbidity and mortality can alter dramatically The smog disaster of 1952 is the most recent and alarming example, but the medical statisticians at the General Register Office from Farr to Logan (1953) have reported fogs in London which have been associated with excesses in mortality ranging from a few hundreds to four thousand

Reviewing the experience of the years 1870–91, Russell (1926) concluded that the sudden rise in the respiratory-disease death-rate noted in the fogs of that period were more likely to be due to the drop in temperature which always accompanied these fogs than to any other environmental characteristic But when the temperature falls, other changes in habit and environment occur for instance, fires are stoked up and there is an increase in the atmospheric pollution The peak of mortality during the London fog of 1952 was much more closely associated with a rapid increase in air pollution, measured by the sulphur-dioxide content of the air, than with contemporary changes in temperature or humidity (Wilkins 1954)

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* The second Milroy lecture for 1957, delivered before the Royal College of Physicians of London on Feb 7, 1957 The first lecture appeared last week.

The critical question seems to be whether these outbreaks of respiratory mortality are the morbid results of the climatic changes alone, or whether pollution has added much to the lethal effects of the physical changes in the atmosphere In other words, is atmospheric pollution the modern equivalent of the *tertium quid* of the epidemiologists before Pasteur—something added to the epidemic situation between individuals and their climatic environment which produces respiratory illness? And if it is, is its effect purely immediate and transient precipitating acute illness or death in men already crippled by respiratory disease? Or does pollution have more chronic insidious effects in those exposed to it?

It should be confessed at once that these questions cannot yet be answered Correlations in time between factors so closely linked as temperature inversion and smoke pollution allow little discrimination between their separate effects But the primary role of epidemiology in the problems of medicine is reconnaissance rather than final resolution And to effect this, one must turn from chronology to a study of the geography of respiratory disease

Geographic Distribution of Respiratory Mortality

In his *Observations*, published in 1750, Short remarks about London that it is " more unhealthy (especially to Children and new Comers) from the Smoaks, Stinks, and close Air ", and elsewhere that " a very moist cold temperature of the Air certainly produces Heaviness, Coughs and other Disorders " It seems fitting that we in the London of today should try to bring Short up to date

The traditional approach to an epidemiological problem is by the analysis of mortality data In London the geographic pattern of respiratory mortality is certainly clear-cut, the death-rate from chronic bronchitis, for example, is more than twice as high in the districts to the north and east of the centre of the City than in other areas such as Hampstead, and Hewitt (1956) has given reasons for thinking that these disparities are due to atmospheric rather than social differences In the country as a whole, the areas of excessive chronic bronchitis mortality have been shown in studies by Pemberton and Goldberg (1954) and Daly (1954) to be those where indices of air pollution are highest These workers do not claim, however, that this is conclusive evidence of cause and effect Death is the terminal event in a chain of circumstances which may each be affected by urban conditions other than atmospheric pollution Thus the multiple contacts of city life may increase the frequency of the minor infections The worst-affected districts of our great towns may be the most heavily plagued by smoke, but they are equally the most congested areas, where men, whose jobs may subject them to industrial dusts, physical exhaustion, and climatic exposure, often live in overcrowded and inadequate homes Although our family studies rather suggest that some of these circumstances may be less important in respiratory infection than had been thought, other social factors such as diet or medical care and duration of convalescence may alter the case-fatality rate of those infections if not their frequency. Mortality-rates may not, therefore, reflect the unalloyed results of the single factor of air pollution, and geographical differences in death-rates should be interpreted with caution

Use of a Standard Occupational Group

An alternative gambit is afforded by the work of the Treasury Medical Service in supervising the health of Civil Servants of all kinds In the General Post Office, for example, postmen are uniformly selected, do much the same job at standard rates of pay, and, once established, form a relatively stable occupational group spending much of their working lives in the same district The cause and timing of all their sickness absences are meticulously recorded, and, should their working lives be cut short by serious disability, the medical standards for retirement on health grounds are continually under the scrutiny of the Treasury Medical Service staff

A review of wastage-rates among postmen due to premature retirement or death because of bronchitis and pneumonia showed a concentration in the great towns and industrial areas of the country There was no gradual increase from South to North such as one might expect if climate in general or temperature in particular were the dominating factors in morbidity Economic and occupational differences cannot explain this geographical pattern of morbidity Other factors to which postmen are exposed as citizens of the great industrial cities must therefore be the determinants of respiratory sickness, and the experience of this standard occupational group may give suggestive clues about their nature and numerical importance

We might consider, for example, that postmen on their rounds in the different parts of London are reasonably equal in all other material respects If so, we can use their sickness experience as an index, free from the influence of social background and occupation, of the effect of local environment on respiratory disease A Meteorological Office publication (Marshall 1952)—*A Century of London Weather*—assures us that there is little difference in temperature and humidity between places within the London area such as Kew, Kingsway, Croydon, and Greenwich, if anything it is warmer in the centre of London Yet the invaliding-rates from chronic bronchitis for London postmen rise steadily from south-west to north-east presenting the same concentration as the male mortality from bronchitis—and, incidentally, from cancer of the lung (Reid 1956, Stocks 1952) Wilkins (1954) reports that this concentration also coincides with the build-up of smoke in the Greater London area by the prevailing west-south-west wind

Thus encouraged, Dr Anthony Fairbairn and I (Fairbairn and Reid 1958) have tried, with the support of Dr W E Chiesman and his colleagues at the Treasury, to exploit the information on sickness among Civil Servants collected either routinely or by special sample surveys We hoped that the use of this standard population would control at least some of the variables involved without restricting unduly the relevance of our findings in these particular groups to the generality of the population

Local Levels of Presumptive Air Pollution and Bronchitis

Before the 1939–45 war, Durst (1940) organised a survey of atmospheric conditions at observation points scattered widely over the country Night and morning, observers noted the range of clear vision and classified conditions in their area according to the frequency and density of mist and fog Analysis showed that areas are quite consistent in their relative fogginess from one year to another Moreover, visibility indices of this type can be shown to be correlated with measures of pollution such as the sulphur-dioxide content of the air and indirect measures such as the index developed by Daly (1954) for county boroughs on the basis of coal consumption per acre of inhabited area.

The country can be divided into groups of areas where the postman's environment at work is fairly homogeneous—e.g., the towns and villages of East Anglia, Scotland outside Glasgow, or the industrial conurbation round Manchester. Wastage-rates due to premature retirement or death because of bronchitis and pneumonia were worked out on the basis of routine reports on such cases among the postmen working in thirty-seven such areas in the United Kingdom. A sample survey of sickness absence by cause allowed us to compute rates due to all forms of respiratory and other disease among these postmen and indoor workers of each sex in the same areas. From the information given in the Registrar-General's reports we calculated death-rates from bronchitis, pneumonia, pulmonary tuberculosis, and cancer of the lung among men and women aged 45–64 in the general population of the same thirty-seven areas. At the same time we collected data on other indices of local environment—population density and domestic overcrowding—likely to be relevant to the incidence of respiratory disease. All these observations related to periods round the 1951 Census.

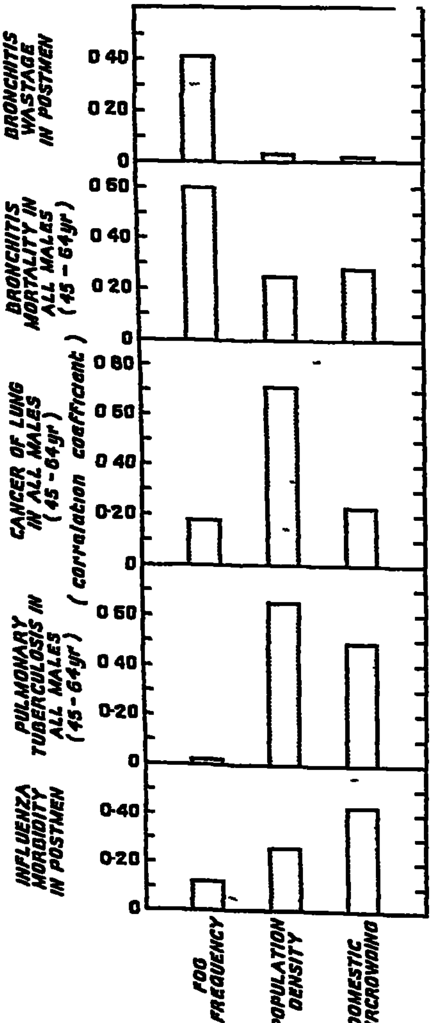

Fig. 5—Net correlation of respiratory disease experience and local environmental indices.

An analysis of the interrelations of some of these rates of respiratory sickness or death with the indices of local environment gave the results shown in fig. 5. The wastage-rates due to postmen dying or retiring prematurely because of bronchitis are uniquely and quite closely related to the frequency of thick and presumably polluted fog, but not to population density or domestic overcrowding, in the same area. An important feature of these results is the consistency between this pattern among men of the same occupational group throughout the country, and the behaviour of bronchitic mortality in middle-aged men in the population as a whole. Again, the death-rates in the general population from cancer of lung, and to some extent from pulmonary tuberculosis, are related not to fog frequency but to population density. This conformity in pattern between lung cancer and phthisis may be an expression of urban rural differences in cigarette smoking, which has been shown to be associated with death from both these diseases (Doll 1953, Lowe 1956). On the other hand, both pulmonary-tuberculosis mortality in the general population and influenza morbidity among postmen rise in step with the degree of domestic overcrowding in the areas, presumably as a result of increased opportunities for cross-infection in both these diseases. If this interpretation of these correlations is correct, it would seem that the regional distribution of bronchitis morbidity and mortality is more readily explained by local differences in fog frequency than by factors such as smoking habits or cross-infection which affect the incidence of lung cancer or pulmonary tuberculosis and other respiratory infections such as influenza.

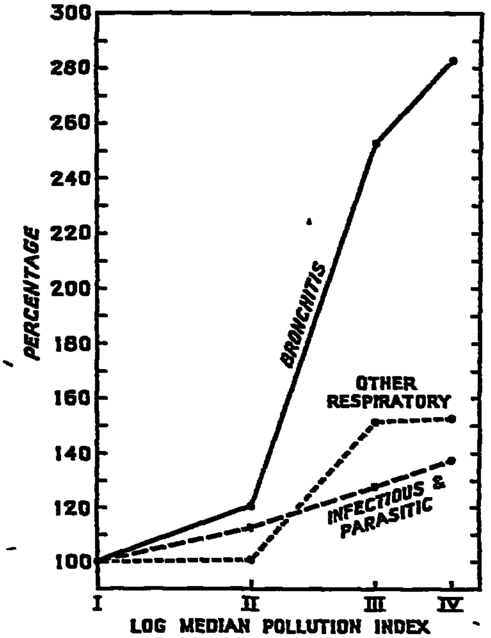

Fig. 6—Absence-rates among postmen working in areas with different air-pollution levels.

It seems reasonable, therefore, to regard the frequency of fog thick enough to restrict visibility to less than 1100 yards as a practical index of those atmospheric conditions which are related to high bronchitis sickness and death rates. But it would be less reasonable to assume that the relation was either simple or direct, for the gradient noted is largely one between small towns and major industrial cities, whose sickness experience may differ for other reasons than atmospheric pollution and in other ways than in the toll of chronic bronchitis.

A more detailed analysis of the sickness experience of postmen working in different areas can give some evidence on these points. The thirty-seven areas can be divided into groups, equal in the size of their postman population, but ranged in increasing steps of the fog index. The crude attack-rates among postmen in those groupings during the years 1946–53 inclusive for some major diagnostic catewith a rapid increase in air pollution, measured by the sulphur-dioxide content of the air, than with contemporary changes in temperature or humidity (Wilkins 1954)

The critical question seems to be whether these outbreaks of respiratory mortality are the morbid results of the climatic changes alone, or whether pollution has added much to the lethal effects of the physical changes in the atmosphere In other words, is atmospheric pollution the modern equivalent of the *tertium quid* of the epidemiologists before Pasteur—something added to the epidemic situation between individuals and their climatic environment which produces respiratory illness? And if it is, is its effect purely immediate and transient precipitating acute illness or death in men already crippled by respiratory disease? Or does pollution have more chronic insidious effects in those exposed to it?

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A comparison of the frequency and severity of attacks of bronchitis during the working lives of bronchitic invalids and their matched controls showed that, even in early adult life, those destined to become disabled by chronic bronchitis have more and longer absences from this cause than other men of the same age (Reid and Fairbairn 1958) The same general trend is equally apparent in the frequency of absence due to colds and other upper respiratory infections, and there is evidence among these bronchitic invalids of a minority who manifest an unusual susceptibility to respiratory infection at least twenty years before they die or have to stop work (usually in their middle fifties) If this long-term predisposition to respiratory illness extends back, as seems likely, to earlier childhood, then in chronic bronchitis, as in so much else, the child is father to the man

Regional Variations in Natural History

Age-trends in both sickness-absence and death-rates from chronic bronchitis agree in emphasising the rapid deterioration which sets in after the age of 45, and fig 8 suggests that the speed of disease evolution may be related to local levels in presumptive air pollution A more detailed comparison of the frequency, duration, and complications of attacks of respiratory illness among these bronchitic postmen showed that, after 45, men working in the more heavily polluted districts of the country had more frequent absences from work and lost more time over the year than did their colleagues in the less affected areas Although the overall incidence of minor and major respiratory infections may not be very different, the attack-rate of pneumonia and pleurisy is 30% higher in the critical age group of 45–54 in the more heavily polluted districts

Reviewing this pattern of respiratory disease makes it seem likely that the exposure to minor infection is not very different in the four groups of areas, but that the cumulative effect of atmospheric pollution transmutes minor infections in later life into major illnesses which appear as serious colds, bronchitis, pleurisy, or pneumonia Of perhaps greater moment, however, are the disorders of circulation which appear, under various diagnostic labels such as "hypertension" or "myocarditis", as complications in the downward course of cardiorespiratory disease among these postmen The serious prognostic significance of these illnesses is evident in the consistent rise in the proportion of men dying in the service while still on sick-leave This immediate case-fatality rate rises steadily from 3% in the least to 11% in the most heavily polluted areas, and the expectation of life of those who retire on pensions after invaliding is appreciably shorter in these foggy districts of the country

To recapitulate—we have found that in a stable group of men, doing the same job for the same pay under the same conditions of service, there are wide geographic variations in the incidence of disabling respiratory disease These variations cannot be explained by social, economic, or occupational factors or by any consistent difference in climate other than fog Not only do more postmen become disabled by chronic bronchitis in areas where thick and presumably polluted fog is more frequent, but the character and natural history of the disease in these areas reflects variation in atmospheric pollution In the most heavily polluted areas of the country—mainly the industrial cities—minor infections among younger bronchitics do not appear to be much more frequent than elsewhere But among the older bronchitic postmen in polluted areas, these minor infections lead to more frequence absence from work and seem more often to lead on to complications such as pleurisy, pneumonia, and circulatory failure which hasten death

Smoking Habit as a Complicating Factor

One of the most striking features of mortality from chronic bronchitis in this country is the pronounced male excess in middle life This excess might be attributed to the occupational circumstances of men's lives, which may expose them to the weather, to hard physical exertion, or to many sources of infection Again, these differences apparent in mortality may reflect differences in case-fatality rate rather than in disease incidence In the Civil Service, however, we have men and women working side by side in the same offices doing the same job and exposed, at least through their working hours, to the same environmental conditions Comparison of attack-rates calculated for men and women indoor office workers in different age-groups but all exposed to the fairly uniform climate of London showed that the excessive mortality of the male is paralleled by an increased morbidity-rate in middle life which cannot be explained by differences in occupation between the sexes (Reid 1956), and Higgins (1957) has reported a similar male excess in the prevalence of bronchitic symptoms in a country district

The differing clinical responses of fathers and mothers to infection noted in the Paddington survey (Brimblecombe et al 1958) certainly suggested that in early adult life the female is more susceptible to respiratory infection than the male The opposite could conceivably hold in later life, but, as Oswald and Medvei (1955) have shown in the same occupational group of Civil Service clerks, the sex disparity is more likely to be explained in part by differences in smoking habits In the longitudinal study already described, there was evidence in the sickness records and death certificates of men followed up for some years of an excessive incidence of peptic ulcer, cancer of the lung, and coronary thrombosis—all conditions already linked by numerous studies with cigarette smoking When taken together with the more direct evidence produced by Doll and Hill (1956) on the consistent upward trend with increased cigarette consumption among doctors in mortality from chronic bronchitis, these results must increase suspicions about the aggravating effect of cigarette smoking in chronic bronchitis and the importance of differences in smoking habits as a source of local variation in mortality from this disease

Prospect for Research

Arnott (1954), speaking as a clinician, has generously referred to the extension of the epidemiological approach beyond the infectious fevers as "the most exciting feature of current medical science" I should like to believe that this was so, but I must admit to the charge that epidemiological studies are apt to raise more questions than they answer The pilot work I have described establishes no more than a prima-facie case for further study of the undoubted association between sickness and death from chronic bronchitis and the frequency of dense and presumably polluted fog in the same area It would be premature to revive the penalty imposed on a citizen of Southwark in the year 1370 who was indicted for "causing a filthy and fulginous vapour by burning raw coal" (He was

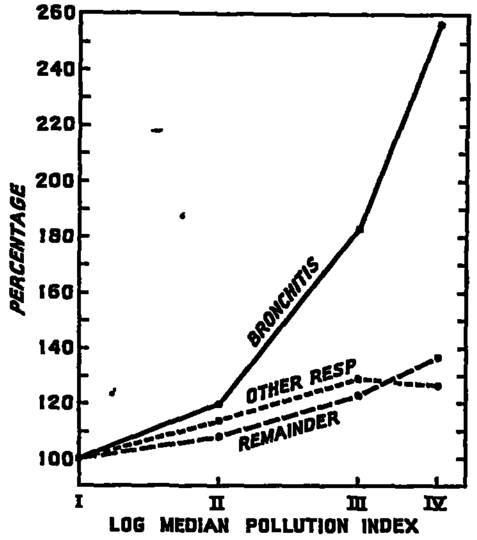

Fig 7—Ratios of absence-rates for postmen and clerks according to local levels of air pollution

gories are set out in fig 6 The gradient between the fog group rates (expressed as ratios to the basic level in the least foggy areas) is much more distinct for bronchitis than for all other respiratory diseases

Although there is a rise in the incidence of the group of specific infectious and parasitic diseases, it is hardly great enough to suggest that a generally increased opportunity for infection in the larger towns fully explains the high bronchitis-rates there There is also some reason to believe that lower morale in the larger post offices may be reflected in higher sickness-rates, but there seems to be no very good reason why chronic bronchitis should be consistently singled out as the excuse for unwarranted absence only in the fog-ridden areas

The most convincing evidence that the excessive chronic-bronchitis rate in the industrial centres is not an illusory reflection of morale but a substantial physical phenomenon comes from a comparison of the experience of postmen and clerks or of postmen of different ages working in the various regions of the country Because of the differing physical demands of their jobs, the same degree of disability due to sickness or injury must inevitably incapacitate the postman more than the clerk Even if the incidence of chronic bronchitis were exactly the same in these two occupational groups, some difference in the frequency of absence from work for that cause would be expected On the other hand, both groups face the infective risk and psychological background common to all inhabitants of the same area If, then, regional variations in air pollution played no part in the onset of bronchitis, this relative disparity between the attack-rates among postmen working largely out of doors and clerks working inside should be the same all over the country When, however, the absence-rates attributed to chronic bronchitis for postmen are compared as a ratio to those of clerks in each of the four pollution groups in turn (fig 7), it becomes quite clear that the gap between the rates widens with each increase in the index of pollution There is no such steep gradient either for other respiratory diseases or for all the remaining causes of absence In short, the increasing frequency of smog is associated with relatively more frequent attacks of bronchitis among the postmen, who are more exposed by their active outside job to that polluted atmosphere, than among the sheltered indoor clerks

What may be the cumulative effects of differences i exposure to polluted atmosphere also appears in the age specific attack-rates of chronic bronchitis among postme of the same age but working in the four pollution group of areas Beginning as early as the age-group 25–34, th gap between the age-specific rates widens increasingl with age Atmospheric pollution may thus have som initiating or persistently aggravating effect on chron bronchitis quite apart from its action on the cardiac o respiratory cripple in the acute smog episode In New Zealand Eastcott (1956) showed that immigrants from thi country who had lived here for the first thirty years o life had higher death-rates from cancer of the lung tha the New Zealand born population of British stock, and the increasing gap in bronchitic incidence here observe may be another result of prolonged exposure to Britis conditions—among them the atmosphere of British towns

Evolution of Chronic Bronchitis

Up to this point I have taken cross-sectional snapsho of the sickness experience of men of different ages durin a relatively short period Chronic bronchitis, however, i a disease whose often slow progress must be studied as i develops over the life-time of the individual Longi- tudinal records of this kind covering the whole of life ar seldom, if ever, available, but in the Post Office each man's detailed sickness history over his entire service is kept i his personal file Thus it was possible to compare the sickness experience of postmen who had been invalided from the postal service because of chronic bronchitis or who had died prematurely because of that disease with that o matched " controls " These " controls " were other postmen, randomly selected from those of the same age, working from the same office, but without completely disabling respiratory disease The intention was to see how the natural history of respiratory illness during adult life o men ultimately disabled by bronchitis differed from the frequency and nature of respiratory illness of other men, not so disabled, working in the same environment At the same time, it should be possible to contrast the develop-

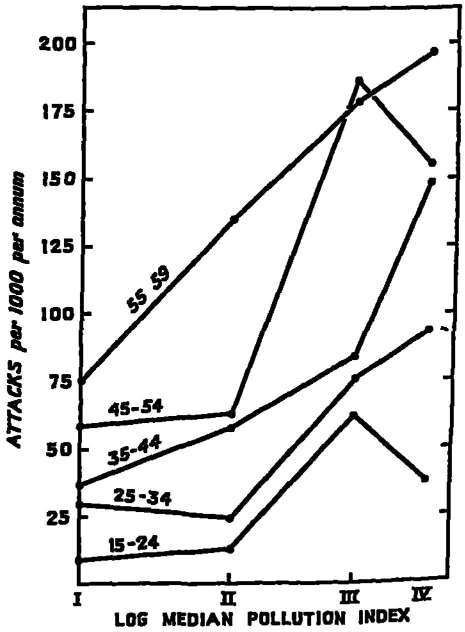

Fig 8—Bronchitis absence-rates at different ages for postmen in areas with different air-pollution levels

ment and character of the disabling disease labelled as "chronic bronchitis" in postmen working in areas of differing degrees of pollution.

A comparison of the frequency and severity of attacks of bronchitis during the working lives of bronchitic invalids and their matched controls showed that, even in early adult life, those destined to become disabled by chronic bronchitis have more and longer absences from this cause than other men of the same age (Reid and Fairbairn 1958). The same general trend is equally apparent in the frequency of absence due to colds and other upper respiratory infections, and there is evidence among these bronchitic invalids of a minority who manifest an unusual susceptibility to respiratory infection at least twenty years before they die or have to stop work (usually in their middle fifties). If this long-term predisposition to respiratory illness extends back, as seems likely, to earlier childhood, then in chronic bronchitis, as in so much else, the child is father to the man.

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Reviewing this pattern of respiratory disease makes it seem likely that the exposure to minor infection is not very different in the four groups of areas, but that the cumulative effect of atmospheric pollution transmutes minor infections in later life into major illnesses which appear as serious colds, bronchitis, pleurisy, or pneumonia. Of perhaps greater moment, however, are the disorders of circulation which appear, under various diagnostic labels such as "hypertension" or "myocarditis", as complications in the downward course of cardiorespiratory disease among these postmen. The serious prognostic significance of these illnesses is evident in the consistent rise in the proportion of men dying in the service while still on sick-leave. This immediate case-fatality rate rises steadily from 3% in the least to 11% in the most heavily polluted areas, and the expectation of life of those who retire on pensions after invaliding is appreciably shorter in these foggy districts of the country.

To recapitulate—we have found that in a stable group of men, doing the same job for the same pay under the same conditions of service, there are wide geographic variations in the incidence of disabling respiratory disease. These variations cannot be explained by social, economic, or occupational factors or by any consistent difference in climate other than fog. Not only do more postmen become disabled by chronic bronchitis in areas where thick and presumably polluted fog is more frequent, but the character and natural history of the disease in these areas reflects variation in atmospheric pollution. In the most heavily polluted areas of the country—mainly the industrial cities—minor infections among younger bronchitics do not appear to be much more frequent than elsewhere. But among the older bronchitic postmen in polluted areas, these minor infections lead to more frequence absence from work and seem more often to lead on to complications such as pleurisy, pneumonia, and circulatory failure which hasten death.

Smoking Habit as a Complicating Factor

One of the most striking features of mortality from chronic bronchitis in this country is the pronounced male excess in middle life. This excess might be attributed to the occupational circumstances of men's lives, which may expose them to the weather, to hard physical exertion, or to many sources of infection. Again, these differences apparent in mortality may reflect differences in case-fatality rate rather than in disease incidence. In the Civil Service, however, we have men and women working side by side in the same offices doing the same job and exposed, at least through their working hours, to the same environmental conditions. Comparison of attack-rates calculated for men and women indoor office workers in different age-groups but all exposed to the fairly uniform climate of London showed that the excessive mortality of the male is paralleled by an increased morbidity-rate in middle life which cannot be explained by differences in occupation between the sexes (Reid 1956), and Higgins (1957) has reported a similar male excess in the prevalence of bronchitic symptoms in a country district.

The differing clinical responses of fathers and mothers to infection noted in the Paddington survey (Brimblecombe et al. 1958) certainly suggested that in early adult life the female is more susceptible to respiratory infection than the male. The opposite could conceivably hold in later life, but, as Oswald and Medvei (1955) have shown in the same occupational group of Civil Service clerks, the sex disparity is more likely to be explained in part by differences in smoking habits. In the longitudinal study already described, there was evidence in the sickness records and death certificates of men followed up for some years of an excessive incidence of peptic ulcer, cancer of the lung, and coronary thrombosis—all conditions already linked by numerous studies with cigarette smoking. When taken together with the more direct evidence produced by Doll and Hill (1956) on the consistent upward trend with increased cigarette consumption among doctors in mortality from chronic bronchitis, these results must increase suspicions about the aggravating effect of cigarette smoking in chronic bronchitis and the importance of differences in smoking habits as a source of local variation in mortality from this disease.

Prospect for Research

Arnott (1954), speaking as a clinician, has generously referred to the extension of the epidemiological approach beyond the infectious fevers as "the most exciting feature of current medical science". I should like to believe that this was so, but I must admit to the charge that epidemiological studies are apt to raise more questions than they answer. The pilot work I have described establishes no more than a prima-facie case for further study of the undoubted association between sickness and death from chronic bronchitis and the frequency of dense and presumably polluted fog in the same area. It would be premature to revive the penalty imposed on a citizen of Southwark in the year 1370 who was indicted for "causing a filthy and fulginous vapour by burning raw coal". (He was hanged) On the other hand, the human and economic consequences of neglect of the environment in the problem of chronic bronchitis are such that any lead, however tenuous, must be followed up

Measurement and comparison are at the basis of epidemiology, and improved nosography is the first step in that splitting of the problem into manageable parts which is essential to its solution Vital statistics deal with chronic bronchitis as a single clinical entity, yet the bronchitis of the young female in a country district may be an allergic response quite different from the infective, rapidly progessive, and disabling disease of the older male in the polluted and congested city The evidence from the study of the invalid postmen certainly suggests that one or more factors in urban environment or habits do twist the clinical pattern into something different and more lethal The classification of respiratory disorders and the standardisation of diagnostic criteria are clearly first needs for any intelligent comparison of experience in different countries and even in different parts of the same town

If we discount the uncontrollable elements of our island climate such as sudden changes of temperature and humidity, we must still identify the hazardous element in the polluted fog of industrial cities If the operation of the Clean Air Act succeeds in removing the solid content of city smoke, will any remaining sulphurous and other gaseous elements continue the erosion of the bronchi of the next generation? Perhaps we must wait, but we should also watch

Although the enhanced risks of infection in the crowded towns cannot explain more than part of the excessive morbidity and mortality from chronic bronchitis, pollution may aggravate infection to produce a much more complex and crippling disease The analogy of the coaction of dust and tuberculous infection in progressive massive fibrosis in miners is apposite, and the methods of field study which are proving so profitable in that condition should be employed in a much wider study of the nature of chest disease following different exposures to atmospheric pollutants

Air pollution produced by burning raw coal is not, however, the only external factor likely to be involved in chronic bronchitis Quite apart from the specific occupational hazards, which I have not discussed, differences in personal smoking habits may explain some of the disparity between town and country and more of the difference between the middle-aged male and female We thus need precise sample surveys of the smoking habits of men and women doing the same job in town and country to see whether, for example, the prevalence of chronic bronchitis is the same in men and women non-smokers living in the same environment Again, cigarette smokers in the fog-ridden towns may have the unduly high bronchitis-rates which some cumulative synergism of personal and atmospheric smoke pollution might produce This is the sort of question which can be answered only by surveys and long-term follow-up

In presenting this catalogue of uncertainties, I am quite unabashed by the dismissal of some earnest students of geology by Sir Joseph Banks, the one-time despotic president of the Royal Society They asked his leave to circulate a series of questions of moment His curt response was that a few fools could ask more questions in half an hour than wise men might answer in years

On the contrary, I prefer to draw courage from Sir William Gull's advice to the British Medical Association on the conduct of collective investigations "Nature is very much a Sphinx," he said, "and will answer no question put to her if it be open to evasion" He counselled the committee to put "a definite question, and that being settled, follow it up by another, and so on i series Nature must at last be driven into a corner and b obliged to say 'Yes' or 'No'" That seems to me to b the only course open to us through the maze of chroni respiratory disease, for I am at one with Gull in believin that a question well posed is already half answered

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HÆMOPHILIA-LIKE STATES IN GIRLS *

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THE possibility that a female hæmophilic offspring might result when an ovum carrying the recessive hæmophilic gene in the X chromosome is fertilised by a sperm also containing the defective gene in its X chromosome was pointed out by Piney (1927) No authentic case, however, was found in the extensive and numerous pedigrees collected by Bulloch and Fildes (1911), Birch (1937), and others

When Hutt et al (1948) discovered in a dog a bleeding condition which appeared identical with the human disease, it became possible to test experimentally whether hæmophilia could be produced in the female An affirmative answer was obtained by Graham et al (1949) when they produced female hæmophilic pups by mating a carrier bitch with a hæmophilic male The human counterpart, a female bleeder having a carrier mother and a hæmophilic father, was reported by Israels et al (1951), their patient exhibited the clinical history and the laboratory findings of hæmophilia

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The recent discovery of several types of hæmophilia-like states necessitates reassessment of classical hæmophilia and its related states in women The opportunity of having available for repeated studies several girls with bleeding conditions closely resembling hæmophilia made it possible to obtain additional pertinent information and to permit correlation with published cases

Laboratory Procedures

The details of the procedures used have been described recently (Quick 1957a) Only a few comments, therefore, on the techniques and interpretation will be given here Blood collected with a silicone-coated syringe and needle was transferred to test-tubes similarly coated The tubes were immersed in an ice-bath. All clotting-tests were made in glass test-tubes (13 mm × 100 mm) at 37°C

Whole-blood clotting-time —This test was made, whenever possible, immediately after the blood was collected, because storage of blood in silicone-coated tubes shortens the clotting-time The normal range is 5-10 minutes

Prothrombin-consumption time —By allowing blood to clot under standardised conditions and by determining the prothrombin activity of the serum the thromboplastin generated during clotting is indirectly measured Since the test is empirical, meticulous standardisation is essential

The test-tube containing 1 ml of blood was put in a water-bath at 37 C Exactly 15 minutes after a solid clot had formed the tube was centrifuged and reincubated at 37°C for 45 minutes more The prothrombin time of the serum was determined by blowing 0 1 ml into a mixture of 0·1 ml of rabbit-brain thromboplastin, 0 1 ml of 0 02*M* $CaCl_2$, and 0 1 ml of deprothrombinised oxalated rabbit-plasma, and accurately timing the clotting Since serum lacks fibrinogen and labile factor (factor v), these have to be supplied, rabbit-plasma adsorbed with $Ca_3(PO_4)$ is a satisfactory source of both Neither deprothrombinised human plasma nor fibrinogen solution is satisfactory, because they do not supply sufficient labile factor When the consumption of prothrombin is very low, as in the clotting of blood from a patient with severe hæmophilia or of platelet-depleted plasma, the prothrombin time of the serum is 8 or 9 seconds

This procedure has been designated " basic " to distinguish it from the following modified prothrombin-consumption time tests which measure various thromboplastin precursors more specifically

Thromboplastinogen-activity time —When rabbit-brain extract is heated to 60°C it loses its holothromboplastic potency—i e , it no longer brings about consumption of prothrombin when added to hæmophilic blood (Quick et al 1952) It retains, however, an activity which is similar to that of platelets it causes consumption of prothrombin in normal plasma depleted of platelets but not in hæmophilic plasma A low consumption of prothrombin with this test is observed in both hæmophilias, A and B, but a normal result is obtained in thrombocytopenic purpura and thrombasthenia (Quick 1957b) In making the test 0 025 ml of the rabbit-brain extract heated to 60°C is added to 1·0 ml of blood Except for this step, the procedure is the same as in the basic test

Hæmolysate test —An extract of human erythrocytes has an activity similar to but not identical with that of platelets (Quick et al 1954b) Added to normal platelet-poor plasma it causes a significantly greater consumption of prothrombin than does an extract of platelets Mixed with plasma from a patient with severe hæmophilia it causes no detectable consumption of prothrombin, shown by the minimal serum-prothrombin time of 8 or 9 seconds The addition of minute amounts of a purified preparation of thromboplastinogen or of normal plasma to hæmophilic blood brings about a relatively high consumption of prothrombin By this test the effect of adding 1 part of normal plasma to 1000 parts of hæmophilic plasma can be measured quantitatively (Quick 1957c)

Consumption of prothrombin with added aged normal serum —The addition of 0 1 ml of aged normal serum to 1 ml of hæmophilic blood before clotting causes no improvement in the consumption of prothrombin On the contrary, when aged serum is added to blood from a patient with hæmophilia B, the consumption of prothrombin is strikingly increased (Quick 1957c)

Thromboplastin-generation test —The method of Biggs and Douglas (1953) was used, but modified by using a platelet substitute made according to the method of Bell and Alton (1954) In recording the results the shortest clotting-time was selected The normal range is usually 7–12 seconds

Preparation of thromboplastinogen —The method described by Quick et al (1954a) was used It consists in removing platelets by rapid centrifugation, then adsorbing prothrombin, stable factor, and PTC (Christmas factor) with $Ca_3(PO_4)_2$, and precipitating the active principle by dilution with ice-cold distilled water and saturation with CO_2 The product obtained is highly potent and free from the other known clotting factors, except for traces of labile factor and fibrinogen The agent has been named thromboplastinogen (Quick 1947) in preference to antihæmophilic globulin, the term originally applied to a plasma factor whose activity was postulated to be independent of platelets (Lozner et al 1942) It was pointed out that the factor could also be named prothromboplastin, but that thromboplastinogen was " more euphonious "

Case-reports

Case 1 —A girl born on Sept 29, 1947, was noted to bruise easily in early infancy, but her first serious bleeding occurred at the age of 18 months, when she cut the frenum of her upper lip At 3 years she had a large hæmatoma on the medial aspect of her left thigh and a swollen knee She required several transfusions but was in hospital only six days Dr M H Poindexter, Jr , of Fargo, North Dakota, diagnosed hæmophilia on the basis of a normal prothrombin time and a prolonged clotting-time

These findings were confirmed in August, 1953, when, in addition, a very poor consumption of prothrombin was found No correction was observed when the patient's blood was mixed with that of a known hæmophiliac Physical examination was normal except for old ecchymotic spots, a hæmatoma on her right elbow, and swelling of the sole of her right foot.

On her second visit, in May, 1954, the laboratory results were the same as before, and the only findings on physical examination were the characteristic small hæmatomas and bruises The patient was not seen again until July, 1956 Between her second and third visits she had swelling of her left popliteal area, a wrist, and an ankle The last named prevented her for several days from walking In August, 1954, she had seven teeth extracted Although she was given one transfusion before and one after the extractions, bleeding began on the fourth day and required six transfusions to control She has not had any transfusions since this episode but has had intramuscular bleeding into a thigh, and in November, 1957, an entire arm became swollen after an injury to the elbow

She was last seen in January, 1958, when her blood was extensively studied, and the same tests were run simultaneously on the blood of a patient known to have severe hæmophilia No deformity, enlargement, or limitation of movement of any joint was found , but, when her right knee was flexed, a sharp click was constantly heard True hæmarthrosis was not shown on radiography Most of the severe bleeding was intramuscular, there was neither epistaxis nor hæmaturia

The family history is entirely negative The mother has no tendency to bleed, two brothers and one sister are normal Neither her father nor her mother knows of any bleeding in their families The patient's father, likewise, is entirely normal, and he has three brothers who have no tendency to bleed Especially significant, the patient has a brother three years younger who is entirely normal

The laboratory studies are summarised in tables I–III

Case 2 —This girl was born on June 16, 1949 Since her early history has been published previously (Quick and Hussey 1953a), only the salient facts need be given here Easy bruising was noted at the age of 5 months At the age of 15 months she had swelling of a knee, and a month later of her buttocks At the age of 3 years she had swelling in the calf of her left leg, severe enough to prevent her for several days from walking Later she had pain and swelling of an ankle She was seen by us for the first time in November, 1951, when she had a hæmatoma on her forehead The main laboratory findings were normal clotting- and bleeding-times, a slightly prolonged prothrombin-time (16 seconds), and a very defective prothrombin-consumption time On mixing her blood with that of a patient known to have severe hæmophilia no correction was observed with the prothrombin-consumption test

TABLE I—LABORATORY FINDINGS IN CASE 1 AND FAMILY

Test	Case 1	Brother	Father	Mother	Known hæmophiliac	Normal control
Clotting-time (min)	51	9	8	$8^{1}/_{2}$	45	8
Prothrombin-consumption time (sec)						
Basic	8	28	26	24	8	32
With T A T * reagent	9	26	38	35	8	32
With hæmolysate	8	51	85	92	8	93
With aged serum	8	25	28	22	8	26
Thromboplastin-generation test (sec)						
Subject's plasma	47	9	9	8	51	7
Subject's serum	9	8	7	7	8	7

Studies on patient's brother, father, and mother were made in 1956
Bleeding and prothrombin times were normal in all subjects
* Thromboplastinogen-activity time

The second studies were made in September, 1952, when her parents and brother were also studied Her findings were exactly the same as those obtained a year previously Significantly, both her father and her mother had a slightly prolonged prothrombin-time—$13^{1}/_{2}$ and 13 seconds respectively At this time mixing her blood with that of a hæmophiliac caused some correction

The patient was seen again in July, 1956 During the five-year interval she had a few serious episodes of bleeding She bled for $2^{1}/_{2}$ weeks after the extraction of a tooth She was given one transfusion, which so far has been the only one received Easy bruising continued and appeared to be worse after colds Her ankles occasionally became swollen She had mild epistaxes for 2 weeks On physical examination typical ecchymotic spots with a hard central nodule were found All her joints were normal in size and function

Her family history is entirely negative No tendency to bleed was found in either the father's or the mother's family Two brothers of the patient are well, have never had abnormal bleeding, and have not shown any tendency to hæmorrhage

TABLE II—EFFECT OF MIXING CASE 1'S BLOOD WITH NORMAL AND WITH HÆMOPHILIC BLOOD

Blood	Clotting-time (min)	Prothrombin-consumption time (sec)	
		Basic	With hæmolysate added
Case 1	51	8	8
Known hæmophiliac	45	8	8
Normal control	8	32	93
Case 1+known hæmophiliac*	24	8	8
Case 1+normal control	$5^{1}/_{2}$	28	77
Known hæmophiliac+normal control	6	22	100

* Equal volumes were mixed

The results of laboratory studies are shown in tables IV–VI

Case 3—This girl was born on Aug 7, 1947 She bruised easily but had no serious bleeding until the age of 18 months She was then seen by a physician because of an eye infection Purpura was diagnosed, probably because of numerous ecchymoses Without any apparent cause she had a cerebral hæmorrhage She was in coma and later was paralysed but recovered fairly rapidly During her early childhood she had numerous bleedings from mucosæ, particularly from the gums, throat, and nose To control epistaxis she required at times several transfusions She also had intramuscular bleeding At the age of 6 years she injured her abdomen and a leg in a fall An extensive hæmorrhage involving the knee and calf resulted immediately, later she had sharp crampy abdominal pain After this had subsided she was symptomless for 11 days, when she had gross hæmaturia and epistaxis At the age of 8 years she had a gastrointestinal infection which caused severe bleeding, both hæmatemesis and melæna, five transfusions were given The episodes of bleeding have continued but have become somewhat less frequent Epistaxis and subcutaneous and intramuscular hæmorrhage remain her most common forms of bleeding During her first 10 years of life she received more than two hundred transfusions Trivial injuries often caused serious hæmorrhage Recently she bled into the palm of her hand, causing enough pressure on the ulnar and median nerves to produce serious motor and sensory disturbances In spite of her difficulties she leads a surprisingly normal life, attends school, and keeps up well with her studies She has no ankylosis or joint deformities and no abnormal neurological signs

From the family history it can be deduced that the disease is hereditary She has a brother two years younger who bleeds like her Another brother two years older is clinically entirely normal Neither father nor mother has had abnormal bleeding, and they know of no bleeding in their families

The patient, her brother who bleeds, and the rest of the family have been studied six times since 1953 The results of various tests have remained fairly constant, except the thromboplastin-generation test, which varies, especially in the activity of the serum The data of two recent studies are presented in table VII

TABLE III—EFFECT OF ADDING PURIFIED THROMBOPLASTINOGEN TO PLASMAS OF CASE 1 AND OF KNOWN HAEMOPHILIACS

Subject	*Amount of* thromboplastinogen (ml) added to 1 0 ml of plasma*	Clotting-time (*min*)	*Modified* prothrombin consumption time† (sec.)
Case I	0		8
„	0 005‡	$3^{1}/_{2}$	37
Hæmophiliac no 1	0 005	$3^{1}/_{2}$	32
Hæmophiliac no 2	0	15	9
„ „	0 005	$3^{1}/_{2}$	20

* The native plasma stored in silicone-coated tubes at −20°C was used, which fact explains the short clotting-times
† In addition to the thromboplastinogen 0 1 ml of hæmolysate and 0 001 ml. of aged serum were added to 1 0 ml of plasma
‡ This amount was obtained from 0 05 ml of normal human plasma

Case 4—This girl was born on Oct 25, 1952 Her first serious bleeding was at the age of 9 months, when she cut a lip During the first years of life her growth and weight gain were low, but otherwise she was normal except for bleeding She bruises easily, has bled from her throat, and had hæmatemesis following a blow to her abdomen

Her family history is entirely negative She has a brother older than she and one younger, both are entirely normal Her father and mother have never had abnormal bleeding, and their families have no record of bleeders

The patient and her parents were only studied once The data are recorded in table VIII

Results

Case 1

The laboratory findings in case 1 are identical with those obtainable in true hæmophilia of the severest type (table I) No consumption of prothrombin can be demonstrated even with as sensitive a procedure as the hæmolysate test The lack of correction in the consumption of prothrombin, when aged normal serum is added to the blood before clotting, localises the defect in the plasma, this localisation is confirmed by the thromboplastin-generation test The close similarity between the

TABLE IV—LABORATORY DATA OF CASE 2 AND FAMILY

Test	Case 2	Youngest brother	Other brother	Father	Mother	Known hæmophiliac	Normal control
Clotting-time (min)	10	8	6*	9	7	45	8
Prothrombin time (sec)	16	$12^{1}/_{2}$	13	12	13	12	12
Prothrombin-consumption time (sec)							
Basic	11	26	35	25	$17^{1}/_{2}$	8	32
With T A T reagent	11	35	22	35	34	8	32
With hæmolysate	41	53		150	120	8	90
With aged serum	26	31		24	25	8	34
Thromboplastin-generation test (sec)							
Subject's plasma	9	9		11	14	45	10
Subject's serum	25	59		20	21	9	10

* Studies were made in November, 1952

TABLE V—EFFECT OF MIXING CASE 2'S PLASMA WITH PLASMAS FROM SEVERE HÆMOPHILIA

Plasma	Prothrombin-consumption time (sec.)
Case 2	11
Known hæmophiliac no. 1	8
,, ,, no. 2	8
,, ,, no. 3	8
Case 2 + hæmophiliac no. 1	16
,, + ,, no. 2	17
,, + ,, no. 3	14

patient's and hæmophilic blood is further shown by the lack of mutual correction when the two bloods are mixed, no consumption of prothrombin can be demonstrated even when hæmolysate is added before clotting (table II). When either the patient's or hæmophilic blood is mixed with normal blood, a significant correction takes place, measured by the prothrombin-consumption test, and the effect is quantitatively about the same. The strongest evidence known for concluding that the coagulation defect in the patient's blood is identical with that in true hæmophilic blood is the correction effected by adding even a minute amount of a purified preparation of thromboplastinogen to her blood. It will be observed from table III that 0·005 ml. of the preparation obtained from 0·05 ml. of normal plasma, when mixed with 1·0 ml. of her native plasma, increased the prothrombin consumption from 8 to 37 seconds. This correction corresponds quantitatively to that obtained when the same amount is added to hæmophilic plasma.

As in true hæmophilia the girl's bleeding-time, prothrombin-time, and platelet-count are normal. Her clinical history, likewise, corresponds to that usually obtained in classical hæmophilia. Epistaxis and other types of mucosal bleeding are absent or infrequent, whereas deep intramuscular hæmorrhages almost invariably follow injury, unless aborted by such means as cold and pressure. On the basis of the much prolonged clotting-time and the almost complete absence of prothrombin consumption, she should be classed as having severe hæmophilia. Her tendency to bleed has remained relatively mild. Although one may conclude from the history that she has had hæmarthroses, no permanent injury has been done to any joint.

TABLE VI—EFFECT OF LABILE AND STABLE FACTORS ON CASE 2'S PROTHROMBIN-TIME

Plasma	Prothrombin-time (sec.)
Case 2	16
Case 2 + labile factor*	15
Case 2 + aged serum†	11
Normal control	11½
Case 2 + normal control (1 : 1)	11

* 0·01 ml. of rabbit plasma adsorbed with Ca₃(PO₄)₂ added to 0·1 ml. of case 2's plasma.
† 0·01 normal aged serum added to 0·1 ml. of case 2's plasma.

Case 2

The laboratory findings in case 2 (table IV) are strikingly different from those in case 1. The clotting-time is only slightly prolonged, but the prothrombin-time is definitely prolonged. The prothrombin-consumption time and the thromboplastinogen-activity time are as abnormal as in mild hæmophilia. The addition of either hæmolysate or normal aged serum to the blood before clotting brings about normal consumption of prothrombin. The generation of thromboplastin, measured by the test of Biggs and Douglas (1953), is strikingly low, and the defect is in the serum. On mixing her native plasma with the plasma of a known hæmophiliac a mutual correction is obtained (table V). Her prothrombin-time appears to be fixed at 15 or 16 seconds, it is not shortened by adding labile factor but is corrected by adding aged normal serum. When an equal volume of her plasma is mixed with fresh normal plasma, the mixture has a normal prothrombin-time (table VI).

TABLE VIII—LABORATORY RESULTS IN CASE 4 AND HER PARENTS

Test	Case 4	Father	Mother
Clotting-time (min.)	8	8	5½
Prothrombin-time (sec.)	12	11½	11½
Bleeding-time (min.)	30–		
Prothrombin-consumption time (sec.)			
Basic	12½	21	20
With T.A.T. reagent	12½	22	42
With hæmolysate	12	77	135
With serum	13	22	20
Thromboplastin-generation test (sec.)			
Subject's plasma	39	11	11½
Subject's serum	7	7	9

From the data in table IV it may be observed that both her parents and two brothers show abnormalities. All have a slightly prolonged prothrombin-time except the father, but he has shown this abnormality at other times. The abnormality is best shown by the thromboplastin-generation test. Interestingly, her youngest brother has a thromboplastin-generation time which is even more abnormal than hers although he is not a bleeder.

Case 3

This case, like cases 1 and 2, belongs to the hæmophilia-like group. Both the prothrombin consumption and the thromboplastinogen-activity time are distinctly abnormal (table VII). The most striking finding is the very prolonged bleeding-time. Curiously, the results of the various clotting-tests are not constant. The clotting-time is sometimes prolonged but often normal. Sometimes the additions of hæmolysate and of serum cause a fair increase in prothrombin consumption but at other times they have only a slight effect. The thromboplastin-generation test

TABLE VII—LABORATORY RESULTS IN CASE 3 AND HER FAMILY

Test	Case 3		Younger brother*		Older brother		Father		Mother		Normal control
	July, 1956	May, 1957	July, 1956	May, 1957	July, 1956	May, 1957	July, 1956	May, 1957	July, 1956	May, 1957	
Clotting-time (min.)	14	9½	3–	9½	9	8	6½	9	8	9	5–10
Prothrombin-time (sec.)	12	12	12	12	12	12	12	12	12	12	12
Bleeding-time (min.)	30–	30–	30–	30–		3		3		3	1–3
Prothrombin-consumption time (sec.)											
Basic	12	13	11	10	35	22	18	14	26	17	16–35
With T.A.T. reagent	12	10	10	9		18		25		27	16–35
With hæmolysate	21	43	27	20		100		70		70	45–90
With aged serum	16	23	15	15		27		28		27	16–35
Thromboplastin-generation test (sec.)											
Subject's plasma	24	34	40	40	8	14	9½	14	8½	15	8–10
Subject's serum	10	15½	9½	17	9½	17	8½	13	8½	13	8–10

* A bleeder with a clinical history very similar to that of case 3

is constantly abnormal, and the defect resides in the plasma Occasionally, however, the serum also seems to be defective

The hereditary pattern can be discerned from table vii The thromboplastin-generation test of the parents is at times abnormal Since both the girl and one of her brothers have identical clinical and laboratory findings, it appears quite certain that the disease is hereditary

Discussion

The occurrence of hæmophilia in the female can be accepted because a sufficient number of cases have been published which meet the diagnostic requirements clinical history, specific laboratory findings, and correct hereditary pattern

The cases reported by Israëls et al (1951) and Pola and Svojítka (1957) are typical

The patient of Taylor and Biggs (1957), who comes from a hæmophilic family and has a bleeder brother, has a normal son This makes it improbable that both X chromosomes are defective

Fantl and Margolis (1955) reported a female, with mild hæmophilia, who has a son who bleeds very easily, his blood closely resembling that of hæmophilia

The patient of Choremis et al (1956), a little girl, likewise appears to be a true hæmophiliac Unfortunately, the family history was unobtainable

Some cases—e g , that reported by Beller and Koch (1956)—do not correspond to true hæmophilia clinically mucosal bleeding is rather uncommon in hæmophilia

Hardisty (1957) has reported in a woman a bleeding condition that appears to be Christmas disease

Case 1 is particularly interesting because her blood is indistinguishable from that of true hæmophilia by all known tests It is reasonably certain that the condition is congenital, because she had no serious illness before the discovery of her tendency to bleed If her disease is true hæmophilia, the hæmophilic genes of both X chromosomes must be present Since both her parents are clinically normal, the cause of her condition is best explained by mutation This, to be sure, is speculation, and the proof can only be established by her offspring All her sons should be bleeders and all her daughters carriers, if this assumption is correct

Case 2 particularly illustrates the need for careful laboratory studies to establish a definitive diagnosis Without an accurately performed prothrombin-time test and thromboplastin-generation test one could easily mistake her disease and diagnose it as true hæmophilia especially since her blood does not always effectively correct true hæmophilic blood The prolonged prothrombin-time is not caused by lack of prothrombin or of labile factor A serum factor from normal blood corrects both the prothrombin-consumption defect and the prothrombin time Case 2 corresponds in most respects to that described by Hougie et al (1957) Their patient had a much longer prothrombin time but otherwise closely resembles our case They named the condition the " Stuart clotting defect " The condition resembles that of the patient described by Telfer et al (1956)

Cases 3 and 4 correspond to that first observed by Alexander and Goldstein (1953), Larrieu and Soulier (1953), and Quick and Hussey (1953b). The characteristic findings are the prolonged bleeding-time, the impaired consumption of prothrombin, and the poor generation of thromboplastin, with the defect in the plasma Singer and Ramot (1956) suggest the term " pseudohæmophilia B " for this disease " Pseudohæmophilia A " is the name given to von Willebrand's disease, which is likewise characterised by a prolonged bleeding-time but is transmitted as a dominant Pseudohæmophilia B appears to be inherited as a recessive, only the homozygote being a bleeder

The importance of bleeding in females is emphasised by the increased number of such patients reported recently The desirability of standardisation of the diagnostic tests to differentiate the various hereditary bleeding-diseases in women is obvious because it is a primary requirement for their classification A bleeding disease in a girl is especially serious because little is known about the hæmostatic control of menstrual bleeding Nearly all the cases of women with hæmophilia-like conditions were over twenty years old when they were first studied, suggesting that their bleeding was relatively mild Some of these patients—e g , the one studied by Pola and Svojítka (1957)—have normal menstruation A patient with hyperheparinæmia, whom we (Quick and Hussey 1953c) studied for several years, also has no abnormal menstrual bleeding, although her clotting-time is consistently about an hour The management of a bleeder at the onset of the first menstruation is extremely difficult because so little information has been published and the effect of a coagulation defect on uterine bleeding is unpredictable

Summary

Four girls with congenital bleeding conditions characterised by defective production of thromboplastin are reported

Case 1's disease is indistinguishable from classical hæmophilia, except that the family history is negative

Case 2 has, in addition to defective consumption of prothrombin and defective generation of thromboplastin, a prolonged prothrombin time Her disease is similar or probably identical with the entity recently named " Stuart clotting defect "

Cases 3 and 4 have a normal prothrombin time but a very prolonged bleeding-time, defective consumption of prothrombin, and faulty generation of thromboplastin The suggested name " pseudohæmophilia B " has been tentatively accepted to designate this disease

The differential diagnoses of this group of diseases is discussed, and their clinical and genetic aspects are presented

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IMPORTANCE OF INTRAVENOUS INJECTION OF DIPHTHERIA ANTISERUM

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IT may be regarded as an accepted fact that, when diphtheria is suspected, the patient ought to be injected with antidiphtheritic serum without delay It is indefensible to wait until the result of the bacteriological examination is known The bacteriological diagnosis should only confirm the bedside diagnosis made by the practitioner The desirability of the early injection of antiserum is discussed in more detail by Tasman and Lansberg (1957)

Opinions differ, however, about the best way of injecting antiserum It is generally deemed advisable to inject it intramuscularly and only to resort to intravenous injection in severe cases (Chatterjee 1954, Gorter 1948, Hyman 1948, Cecil and Loeb 1952, Herderschee 1953, Christie 1955) Lepintre (1954) goes so far as to maintain that the antiserum must never be injected intravenously but should always be injected either intramuscularly or subcutaneously

Tasman et al (1954, 1955) have shown that the saliva of diphtheria patients usually contains diphtheria toxin When purified diphtheria antiserum (obtained from horses) is injected intramuscularly, the antitoxin is sooner or later excreted in the saliva via the salivary glands and will then neutralise this toxin Actively immunised persons do not excrete the (homologous) antitoxin in their blood through the salivary glands

We thought it worth while to investigate this excretion of antitoxin through the salivary glands more closely and, more especially, to find if there were any differences in this respect between patients injected intramuscularly and those injected intravenously

Excretion of Antitoxin in Saliva

The saliva of patients was tested for antitoxin at various times after either intramuscular or intravenous injection of purified diphtheria antiserum The results are shown in table I[1]

This excretion of antitoxin in the saliva via the salivary glands is very important Our investigation showed that, after only 30 minutes, the saliva of all but one of the intravenously injected patients already contained antitoxin and had therefore become atoxic[2] In other words, from this moment no more toxin would be absorbed from the saliva flowing over the inflamed and damaged membranes of the tonsils and the pharynx In the intramuscularly injected patients this rapid excretion of antitoxin was exceptional, usually it was a long time before the saliva contained any antitoxin During this interval diphtheria toxin could be absorbed from the saliva through the inflamed membranes of the tonsils and the pharynx

TABLE I—EXCRETION OF ANTITOXIN IN SALIVA

Intramuscular injection (average dose 28,000 A U)		Intravenous injection (average dose 12,000 A U)	
No of cases	Time taken for antitoxin to reach saliva	No of cases	Time taken for antitoxin to reach saliva
1	30 min	12	30 min
3	4–5 hr	1	6 hr
3	10 hr		
9	1–9 days		

This difference between the two groups of patients is the more striking because the intramuscularly injected patients received on the average 2 5 times as much antitoxin as did those injected intravenously

Blood-serum Titres

We took samples of blood from patients before they received the antidiphtheritic serum either intravenously or intramuscularly and at set times after its injection, and determined the antitoxin titres Table II shows the results in a greatly abridged form, the titres are expressed as percentages of the highest titre found

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[1] For lack of space the numerical results of this investigation are given only in summarised form here We hope to publish the full details elsewhere

[2] The first samples of saliva were taken 30 minutes after the serum had been injected It is by no means inconceivable that antitoxin may appear in the saliva of the intravenously injected patients even before that time

TABLE II—ANTITOXIN CONTENT OF BLOOD-SERUM OF PATIENTS INJECTED INTRAMUSCULARLY AND INTRAVENOUSLY

Intramuscular injection

Case no	Dose of antitoxin (A U)	Titres expressed as % of highest titre*											
		Days after injection											
		1	2	4	6	8	10	12	14	16	18	20	22
1	60,000	33	56	100	100	78	67	56	44	33	22	17	11
2	40,000	44	74	100	96								
3	20,000	27	38	100	80								
4	40 000	44	75	100		75	50	25		19	13		5
5	40,000	100	100	67		50	33						
6	20,000	40	60	70	100	80		48		34			12
7	20,000	23	46	92	100	77	53		30	23		20	18
8	20,000	100		85	63		38		21	11	8		
9	20,000	77	100	100	77	50			43	37			
10	20,000	35	83	100	70	56	50		40		20		
11	80 000	30	64	100	64	50	40	24		14	10		
12	20,000	50	80	100	100	70		36		28		26	
13	80 000	23	100	85		40	34	34		18			9
14	20,000	60	96	100	64	54	40	24		14		9	
15	20 000	45	77	100	70	54		37		30			11
16	20 000	56	100	46	46	46		25		25		25	
17	8000	67	100	85	60	47	32	22	22	15	9		
	Mean	50	78	90	78	59	44	33	(33)	23	(13)	(19)	(11)

Intravenous injection

Case no	Dose of antitoxin (A U)	Titres expressed as % of highest titre found*							
		Days after injection							
		1	2	4	6	8	10	12	14
1	10,000	100	89	55	43	43	43	37	17
2	10,000		100	71	43	28	20	14	6
3	10,000	100		66	37	30	30	30	20
4	10,000	100	78	56	56	44	44		22
5	10,000	100	78	56	44	44		11	4
6	10,000	100	82	64	64		25	25	
7	10,000	100	100			63	33	13	
8	10,000	100	55	55	37		10		
9	10,000	100	64	44	33	22	17	13	
10	10,000	100	60	40	30	24	20	16	
11	10,000	100	62	38	25	19	13	7	7
12	10,000	100		56	44	28	17	11	5
13	10 000	100	98	98	58	29	29	21	16
14	10,000	100	90			37	24		17
15	10,000	100	100	25	25	25			10
16	10,000	100		67			30	20	18
17	10,000	100	91	40	40	27	18	14	9
18	10 000	100	50	30	17	10	6	4	3
19	20,000	100	60	40	34	27	18	12	10
20	10,000	100	56	46	37	25	19	11	13
	Mean	100	77	53	39	31	23	16	12

* In these calculations the titres before the injection of antiserum have been subtracted from the titres found after the injection because we are here concerned solely with the course of the antitoxin level resulting from the injection of heterologous diphtheria antitoxin

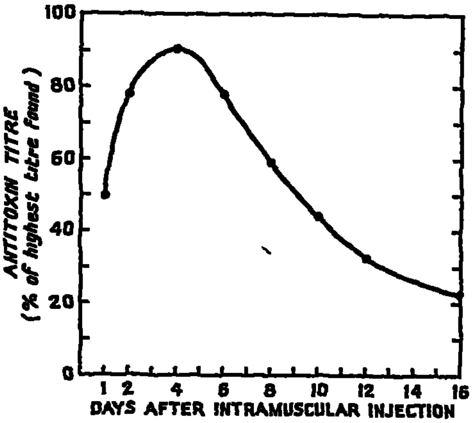

Fig 1—Mean titres of antitoxin in serum after intramuscular injection

The absorption and excretion of antitoxin from antiserum injected either intramuscularly or intravenously varied greatly from one patient to another It is, however, obvious that the antiserum is absorbed much more slowly after intramuscular injection, the highest titre in the serum not being reached until after 2–6 days on the average

The average titres expressed as percentages of the highest titre found are shown after intramuscular injection (fig 1) and after intravenous injection (fig 2)

One is immediately struck by the great similarity between the two curves of antitoxin titres This is brought out even more clearly when the percentage titres (expressed as percentages of the highest titre found) are plotted on a logarithmic scale and in both cases the average titre found 4 days after the injection is taken as 100%[3]

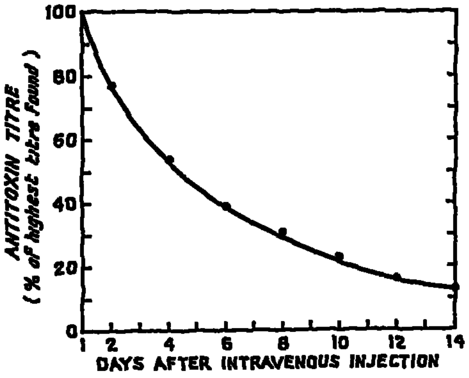

Fig 2—Mean titres of antitoxin in serum after intravenous injection

Fig 3 gives the results of these calculations Here the two lines practically coincide from the fourth day after the injection of the antiserum From this we conclude that the antitoxin in the intravenously injected antiserum is not excreted more rapidly than that in the intramuscularly injected antiserum Hence in this respect there is no reason why the intramuscular injection of antiserum should be preferred to the intravenous Madsen (1936) reached the same conclusion after a similar investigation

In view of these results the obvious thing would have been to test the presumptive superiority of the intravenous method, compared with the intramuscular, on a large number of patients, but such a plan would meet with many difficulties, the chief obstacle being the small number of diphtheria patients available at present For this reason we confined ourselves to experiments with laboratory animals

Design and Application of an "Animal Model"

When a guineapig is injected with a certain number of lethal doses of diphtheria toxin it can be saved from death or protected from typical morbid symptoms by injecting antitoxin before or shortly after the injection of toxin When the quantities of toxin and antitoxin to be injected have been fixed, the interval between the injection of toxin and that of antitoxin will determine the clinical picture If a short interval is chosen, the guineapigs will show only very slight transient symptoms or none at all If a long interval is allowed, most of the guineapigs will show severe manifestations (much loss of weight, severe cardiac manifestations, and paralyses) or most of them will die

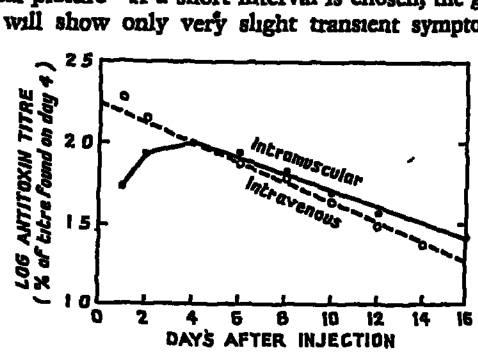

Fig 3—Logarithms of titres of antitoxin in serum after intramuscular and after intravenous injection

In other words, therefore, a suitable choice of the three determining factors—amount of toxin, amount of antitoxin, and length of time between the two injections—will make it possible to control the clinical picture so that special attention can be given to different aspects of it

A well-standardised "animal model" of this kind will also provide an excellent means of ascertaining experimentally the influence of a fourth factor—e g, the route by which the antitoxin is injected

After preliminary experiments we used male[4] guineapigs weighing 300–350 g in all our further investigations These were injected subcutaneously with 5 M L D of diphtheria toxin at the beginning of each experiment A certain number of hours afterwards the guineapigs were injected with 1 antitoxic unit of diphtheria antitoxin, half of them receiving this antitoxin intramuscularly and the

TABLE III—CHANGES OF WEIGHT OF GUINEAPIGS INTRAVENOUSLY OR INTRAMUSCULARLY INJECTED WITH DIPHTHERIA ANTITOXIN

Days elapsed after the injection or serum	Mean weight of guineapigs on consecutive days (g)	
	Intravenously injected	Intramuscularly injected
0	306 (*100%*)	307 (*100%*)
1	316 (*103%*)	307 (*100%*)
2	308 (*101%*)	299 (*97 4%*)
3	305 (*99 7%*)	291 (*94 8%*)
4	291 (*95%*)	286 (*93 1%*)
5	294 (*96%*)	281 (*91 5%*)
6	293 (*95 7%*)	275 (*89 6%*)
7	289 (*94 4%*)	271 (*88%*)
8	289 (*94 4%*)	262 (*85 3%*)
9	286 (*93%*)	255 (*83%*)
10	289 (*94 4%*)	255 (*83%*)
11	293 (*95 7%*)	256 (*83 3%*)

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[3] On the average the absorption of intramuscularly injected serum is complete at the end of this period The subsequent excretion of this intramuscularly injected antitoxin is strictly comparable to that of the intravenously injected antitoxin

[4] The intravenous injection of antiserum is technically much simpler in the male guineapig than in the female The antiserum was injected into a branch of the femoral vein in the subcutaneous tissue of the inside of the thigh

other half intravenously By determining beforehand the time required for the different injections it was possible to ensure that the time between the injection of the toxin and that of the antitoxin was the same for every guineapig in each experiment. In each experiment some guineapigs were injected with toxin only, without a subsequent injection of antitoxin, as controls These controls were always dead on the 2nd or 3rd day after the injection of the toxin.

Experiment I

Two groups of guineapigs received 5 M.L.D of diphtheria toxin subcutaneously, after 9 hours 1 A.U of antitoxin was injected intramuscularly into 15 guineapigs and intravenously into 15 others Of the intramuscularly injected guineapigs 4 died, after 2, 6, 7, and 9 days, whereas 4 of those injected intravenously died after 6, 7, 8, and 10 days All the guineapigs were weighed twice daily, after which the mean weight of each group was calculated Table III gives the results of this experiment, which are graphically represented in fig 4 The initial weight per group is here taken as 100

From these results we may conclude that the guineapigs injected intramuscularly with antiserum showed a greater and more prolonged loss of weight than did those injected intravenously Therefore the general condition of the former throughout the experiment was considerably worse than that of the latter under otherwise identical conditions

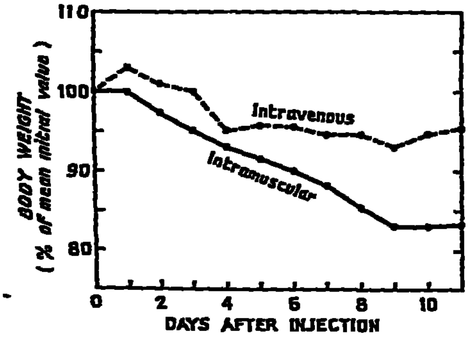

Fig 4—Weights of guineapigs after intramuscular and intravenous injection of antidiphtheritic serum.

Experiment II

If the interval between the injection of toxin and that of antitoxin is long, one may expect a greater number of deaths in both groups of guineapigs To test the difference between the intramuscular and the intravenous injection of antiserum, two groups of 65 guineapigs were subcutaneously injected with 5 M.L.D of diphtheria toxin. After 9½ hours they were given 1 A.U of antitoxin. One group was injected intravenously with the antitoxin and the other intramuscularly The results of this experiment are given in table IV

These figures suggest that guineapigs previously treated with toxin have a considerably better chance of survival when injected intravenously than when injected intramuscularly with the same dose of diphtheria antitoxin.

It may at first sight seem strange that lengthening of the interval between the toxin and antitoxin injections by only 30 min. (from 9 to 9½ hr) should have such a striking effect on the mortality-rate of the guineapigs In experiment I (9 hr interval) only 4 guineapigs died in each of the two groups (about 25%), whereas in experiment II (9½ hr interval) 52% of the guineapigs died in one group and 86% in the other This result is closely related to the experimental conditions If we had chosen different doses of toxin and of antitoxin and a different interval we would have obtained results quantitatively different from these For further general considerations on this "animal model" see below

Experiment III

It was to be expected that the use of a considerably shorter interval between the injection of toxin and that of antitoxin would lead to fewer deaths and provide information about the effect of the method of injection on the paralyses which appear in a later stage of diphtheria

TABLE IV—MORTALITY AMONG GUINEAPIGS INTRAVENOUSLY OR INTRAMUSCULARLY INJECTED WITH DIPHTHERIA ANTITOXIN, DIPHTHERIA TOXIN HAVING BEEN INJECTED 9½ HOURS BEFORE NUMBER OF ANIMALS IN EACH GROUP 65, TOXIN DOSE 5 M.L.D ; ANTITOXIN DOSE 1 A U

Days elapsed after injection of serum	Deaths in each group of 65 daily	
	Injected intravenously	Injected intramuscularly
1	0	7
2	0	0
3	1	1
4	7	6
5	7	6
6	5	4
7	3	5
8	2	5
9	1	2
10	1	6
11	2	4
12	0	6
13	4	2
14	0	1
15	1	1
Total	34	56

For this purpose two groups of 46 and 48 guineapigs were given 5 M.L.D of antitoxin subcutaneously and 6½ hours later were injected either intravenously or intramuscularly with 1 A.U of antitoxin. Table V shows the incidence of paralysis this primarily and chiefly affected the hind legs Fig 5 shows these results

These data show that, under the conditions of the experiment, paralysis came on fairly late after 16 days among the intramuscularly injected guineapigs, and not until after 21 days among those intravenously injected. 32 days after the beginning of the experiment all the intramuscularly injected guineapigs showed unmistakable signs of paralysis, whereas only 33% of those injected intravenously did so

It thus appears that the intravenous injection of antiserum very considerably reduces the chance of the development of postdiphtheritic paralysis These paralyses also appear later than they do after the intramuscular injection of antiserum.

Experiment IV

It is well known that the heart is the organ that suffers most from the harmful effect of diphtheria toxin. Therefore in our efforts to design a well-planned experiment we paid full attention to the heart.

For this purpose two groups of 184 guineapigs were subcutaneously injected with 5 M.L.D of diphtheria toxin. After

TABLE V—INCIDENCE OF PARALYSIS AMONG GUINEAPIGS INTRAVENOUSLY OR INTRAMUSCULARLY INJECTED WITH DIPHTHERIA ANTITOXIN, DIPHTHERIA TOXIN HAVING BEEN INJECTED 6½ HOURS PREVIOUSLY NUMBER OF ANIMALS IN EACH GROUP 46 (INJECTED INTRAVENOUSLY) AND 48 (INJECTED INTRAMUSCULARLY), TOXIN DOSE 5 M.L.D, ANTITOXIN DOSE 1 A.U

Days elapsed after injection of serum	Intravenous injection		Intramuscular injection	
	No of animals with paralysis	Percentage of total number of guineapigs	No of animals with paralysis	Percentage of total number of guineapigs
15	0	0	0	0
16	0	0	1	2·0
17	0	0	2	4·0
18	0	0	6	12·5
19	0	0	11	23·0
20	0	0	19	39·6
21	3	6·5	24	50·0
22	4	8·8	26	56·2
23	8	17·4	29	60·4
24	10	21·7	31	64·6
25	11	24·0	35	73·0
26	11	24·0	39	81·3
27	11	24·0	39	81·3
28	12	26·1	43	89·6
29	12	26·1	44	91·7
30	14	30·5	47	98·0
31	14	30·5	47	98·0
32	15	32·6	48	100·0

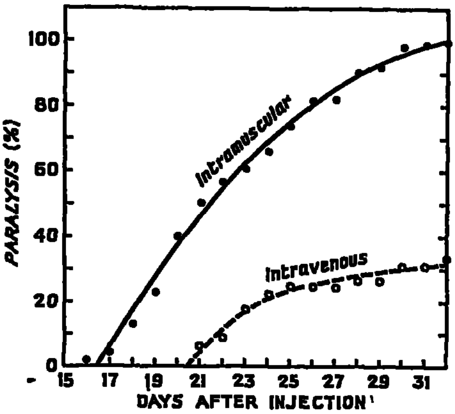

Fig 5—Incidence of paralysis among guineapigs after intramuscular and intravenous injection of antidiphtheritic serum

6$^{1}/_{2}$ hours they all received 1 A U of antitoxin, the first group intravenously and the second intramuscularly After 1, 3, 6, 9, 12, and 15 days about a sixth of the guineapigs in each group were killed, and their hearts were removed and fixed in 20% aqueous solution of formalin The guineapigs which had died spontaneously at the times mentioned were regarded as "killed", and their hearts were treated in the same way Frozen sections were made of roughly the same part of the wall of the left ventricle of each heart For the study of the myocardial lesions these sections were stained with hæmatoxylin-eosin For the demonstration of fatty degeneration separate sections were stained with sudan III

To provide a standard of comparison for the microscopically observed histological changes in the hearts of the treated guineapigs we killed 4 normal non-treated guineapigs per group of killed animals and spontaneous deaths The hearts of these animals were prepared in the same way

This pathological study was organised in such a way that the member of our team who performed the dissections and the microscopic examination (H H V) never knew in advance to which category (injected or non-injected) the various guineapigs belonged Thus an objective appreciation of the material was ensured

As regards myocarditis, the changes observed ranged from very slight local infiltration with mononuclear cells to strong, practically diffuse, infiltration with many mononuclear cells, sometimes accompanied by leucocytes, lymphocytes, or fibroblasts

As regards fatty degeneration of the heart, the mild cases showed only a few fat-globules in a few muscle-fibres In severely degenerated hearts practically all the fibres contained numerous, sometimes fairly large, drops of fat

In this experiment also some control guineapigs were injected with toxin only and not with serum All died within 2 days, their hearts always showing considerable fatty degeneration

The gravity of the lesions microscopically observed in the hearts of the different guineapigs varied greatly and was (more or less quantitatively) classified as ±, +, ++ or +++

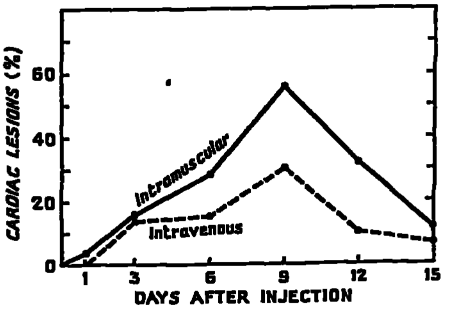

Fig 6—Incidence of cardiac lesions among guineapigs after intramuscular and intravenous injection of antidiphtheritic serum

Occasionally the non-injected controls (neither toxin nor antiserum) also showed slight lesions of the myocardium, classifiable as ± or + This was the case in 15 of the 24 normal non-treated controls Fatty degeneration of the heart was not found in any of the non-treated controls

Some of the treated guineapigs also showed such slight lesions It seemed only logical to leave these slight lesions, also found in non-treated controls, out of account Consequently table VI includes only the grave lesions (myocarditis and fatty degeneration taken together) The data are also shown in fig 6

More or less severe lesions of the heart (myocarditis and fatty degeneration) were found in both groups This is understandable because all the guineapigs had been exposed to the injurious action of 5 M L D of diphtheria toxin for 6$^{1}/_{2}$ hours before they were injected with antitoxin

Under the conditions of the experiment these lesions reached their climax after 9 days, recovery then setting in at the same time in both groups Of course this last circumstance may have been due to chance It is not impossible that, if the experiment were arranged differently, the times of recovery would not coincide

Finally we tried to divide the observed lesions into myocarditis and fatty degeneration

The numerical data and graphs relating to this part of the investigation are not shown here, owing to shortage of space It will suffice to state that the guineapigs injected intramuscularly with antidiphtheritic serum showed more cases of myocarditis and fatty degeneration of the heart than did the intravenously injected ones

TABLE VI—DISTRIBUTION OF SERIOUS LESIONS OF THE HEART FOUND AMONG THE VARIOUS GROUPS OF GUINEAPIGS GIVEN 5 M L D OF TOXIN SUBCUTANEOUSLY, FOLLOWED BY INJECTION OF 1 A U OF ANTITOXIN INTRAMUSCULARLY OR INTRAVENOUSLY AFTER 6$^{1}/_{2}$ HOURS

No of days between serum injection and killing	Intravenously injected		Intramuscularly injected	
	No killed	No of heart lesions	No killed	No of heart lesions
1	30	0	30	1 *(3 3%)*
3	35	5 *(14 3%)*	38	6 *(15 8%)*
6	32	5 *(15 6%)*	31	9 *(29 0%)*
9	29	9 *(31 0%)*	30	17 *(56 6%)*
12	29	3 *(10 3%)*	30	10 *(33 3%)*
15	29	2 *(7 0%)*	25	3 *(12 0%)*

As regards the observed lesions of the heart, there again emerges a clear difference between the results of the two methods, which is strongly in favour of the intravenous injection of antiserum This is easily explained After the injection of intravenous antitoxin the serum of the guineapig is practically immediately "up to titre"—i e, the total amount of antitoxin is available immediately for neutralisation of the toxin still circulating freely at that moment This toxin can then no longer cause a lesion of the heart Possibly part of the toxin which has already penetrated into the myocardium is also neutralised

The effect of the intramuscular injection of antiserum is the same, but slower, because of the comparatively slow absorption of the antitoxin thus injected The toxin still circulating freely is rendered inactive more slowly or can act longer on the myocardium, with all the consequences of this

The difference between the antitoxin titres in the guineapigs injected intravenously and intramuscularly with antiserum will, of course, be greatest in the first few hours This is undoubtedly responsible for the large difference in the incidence of cardiac damage

Summary of Results of Experiments

Groups of guineapigs were subcutaneously injected, 2 at a time, with a constant dose of diphtheria toxin (5 M L D) After a certain number of hours they all received a constant dose of antitoxin (1 A U), half of them being injected intravenously and the other half intramuscularly The intravenous injection of antiserum had a considerably greater therapeutic effect than had the intramuscular The guineapigs injected intravenously with serum showed less loss of weight and more rapid recovery of weight, fewer deaths, less frequent and later development of paralysis, and fewer lesions of the heart (myocarditis and fatty degeneration) than did guineapigs injected intramuscularly

Discussion

The experiments were made under strictly standardised conditions The doses of toxin and of antitoxin injected were the same for all the guineapigs, which were all of the same sex and had the same weight in each pair The time between the injection of toxin and that of antitoxin was the same for each pair In this way we found a quantitative difference between the therapeutic effects of the intravenous and the intramuscular injection of antiserum Had the criteria of these experiments (amount of toxin, amount of antitoxin, and interval between the two injections) been different, we would no doubt have seen the same qualitative differences, but the absolute figures would not have been the same

Obviously the quantitative results obtained with this "animal model" cannot be quantitatively transferred to the therapy of human diphtheria patients The criteria for the latter are different from those applied in the experiment on guineapigs

If, however, the pathogenesis of human diphtheria is determined by the formation of toxin by the diphtheria bacillus infecting the patient and by the effects of this toxin, especially on the heart and the nervous system, we may indeed apply the qualitative results of these laboratory experiments to man

Summarising the results of experiments I–III we may conclude that, for the treatment of human diphtheria also, the intravenous injection of diphtheria antiserum is much to be preferred to the intramuscular route for the following reasons:

(1) After the intravenous injection of antiserum the patient's serum is almost immediately "up to titre"—in other words, the total amount of diphtheria antitoxin is transported very quickly through the blood to the organs concerned Intramuscularly injected antiserum is absorbed only slowly, on the average this absorption is not completed until after 4 days, but it may take as much as 6 days The serum titres of the patients were determined 24 hours at the earliest after the injection of antitoxin, hence we cannot give any figures for the serum-antitoxin levels within a shorter time after the intramuscular or the intravenous injection It can, however, safely be assumed that the relative and absolute differences will be large in the first few hours after the injection

(2) As a non-specific protein, the intravenously injected antitoxin is not more quickly broken down and excreted than intramuscularly injected antitoxin

(3) Very shortly after the intravenous injection of antiserum some of the antitoxin is excreted into the saliva through the salivary glands From this moment the saliva is atoxic, henceforth no toxin can be absorbed from this saliva through the inflamed and damaged tonsils and wall of the pharynx After the *intramuscular* injection of antiserum it usually takes many hours, sometimes even days, for this excretion of antitoxin through the salivary glands to get going During this interval the saliva contains toxin which can be absorbed through the inflamed tonsils and wall of the pharynx.

(4) Lesions of the heart (myocarditis and fatty degeneration) will very probably be less common among intravenously injected than among intramuscularly injected patients These lesions will presumably also be less serious among the former than among the latter

(5) As a group, intravenously injected patients will very probably show fewer cases of paralysis than will intramuscularly injected patients

(6) Under comparable conditions the mortality among intravenously injected patients is likely to be lower than among intramuscularly injected patients

There is no danger attached to the intravenous injection of the antiserum, provided that certain precautions are taken The skin test for hypersensitivity to the antiserum is especially important and should not be omitted

For this test 0 2 ml of the antiserum, diluted to a tenth with saline solution, should be injected intracutaneously on the flexor aspect of the forearm It is absolutely imperative that a weal should form during this injection, if it does not, the intracutaneous injection must be considered unsuccessful and will have to be repeated

If no redness or swelling shows within an hour after the intracutaneous injection, the intravenous injection can safely be given Our experience with many hundreds of patients is that there are then never any serious reactions Some hours after the intravenous injection of serum (enzymatically purified and radically despeciated horse-serum) a few of the patients had slight pyrexia, sometimes accompanied by a rigor This type of reaction proved harmless

If, however, the skin reaction is positive (redness and/or swelling), the serum must be injected intramuscularly and in very small portions at intervals of half an hour or an hour, under the supervision of an experienced person who, if necessary, can administer adrenaline (0 1–1 0 ml of adrenaline hydrochloride 1 1000, according to the patient's age) if the patient shows obvious allergic phenomena

Parish et al (1957) propose a hypersensitivity test in which 0 2 ml of undiluted serum is injected subcutaneously If there is no general reaction within 30 minutes, the whole dose of serum can be injected either subcutaneously or intramuscularly without special precautions This refers to the injection of a prophylactic dose of antitetanus serum (generally 1500 A U in 1 ml)

We do not recommend this procedure for diphtheria patients We believe that the risk of serious allergic reactions is much greater after the subcutaneous injection of 0 2 ml. of undiluted antidiphtheritic serum (4000 A U per ml , the protein content generally being greater than that of prophylactic antitetanic serum) than after the test injection described by us

The doses of antidiphtheritic serum which we have given in the last few years have been 10,000–20,000 A U per patient according to age The results of the determination of antitoxin titres after the intravenous injection have convinced us that an additional intramuscular injection of antidiphtheritic serum would be superfluous

Provided that the precautions described above are observed, there is not the slightest objection to the intravenous injection of antiserum in all cases where an injection may be required Consequently all these patients should be injected not intramuscularly but intravenously with diphtheria antitoxin The intravenous injection of antiserum in patients suspected of diphtheria ought therefore to become the rule and should not be reserved for "serious" or toxic cases, as is still usually done at present

Moreover it is by no means always possible to predict with certainty the course of the diphtheria During an epidemic there have repeatedly been cases which initially seemed mild but became toxic within a few hours and rapidly fatal Some of these patients would probably have been saved if they had been given an intravenous injection of antidiphtheritic serum at the earliest opportunity

It should be borne in mind that, in cases of suspected diphtheria, the first object of the antiserum therapy is the quickest and completest possible elimination of any further absorption of diphtheria toxin (e g, from the saliva) and the binding of the toxin still circulating The investigations here described will have shown that not only the promptness of the injection but also its route can have a decisive effect Not until this has been done will the treatment be directed to combating the damage already done to the heart, kidneys, and nervous system

Summary

An investigation is described which clearly brought out the advantages of the intravenous injection of antitoxic serum in patients suspected of diphtheria, compared with the intramuscular injection still commonly used

The intravenously injected antitoxin immediately brings the patient's serum "up to titre", whereas absorption of the intramuscularly injected antitoxin is slow, usually not being complete until after about 4 days, and sometimes 6 days

Intravenously injected antitoxin is not excreted more rapidly than intramuscularly injected antitoxin

Very shortly after the intravenous injection of antitoxin a small portion of it is excreted through the salivary glands into the saliva, which it renders atoxic Consequently from this moment no more toxin will be absorbed from the saliva through the inflamed and damaged tonsils and wall of the pharynx

The results of experiments on guineapigs indicate that patients intravenously injected with antidiphtheritic serum may be expected to show fewer lesions of the heart (myocarditis and fatty degeneration), fewer post-diphtheritic paralyses, and a lower mortality than patients intramuscularly injected with antiserum

With due observance of the necessary precautions—e g, a skin test for hypersensitivity (which must be negative)—diphtheria antitoxin should be injected not intramuscularly but intravenously whenever such an injection is required, even in mild cases of diphtheria

We are greatly indebted to our colleagues Dr W Smit, Dr J Roos, Dr G L Wilkens, Dr H M van Vessem, Dr A van Dongen, and Dr A M van Rooyen for submitting samples of the saliva and blood from their patients Without their cooperation a considerable part of this investigation could not have been undertaken

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"The only advantage that other animals can be supposed to have over man is, that being excluded by their nature from all mental enjoyments, they are also secured from all the pains and disquietudes that proceed from the same source, but to acquire an exemption from disquietude at the expense of being equally exempted from all the delicate feelings of the mind and affections of the heart, is a purchase which I hope no honest mind will ever be willing to make"—John Moore. *Medical Sketches*, pp 223-4 London, 1786

EPIDEMIOLOGY OF STILLBIRTHS AND INFANT DEATHS DUE TO CONGENITAL MALFORMATION

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The cause of most fœtal malformations is obscure Some types, both animal and human, are inherited and appear in accordance with the mendelian laws The environment of the early embryo may be responsible for other types or may bring out latent tendencies, this has been proved experimentally in primitive animals and some mammals through changes of temperature and pH, mechanical injury, anoxia, dietetic deficiencies, and exposure to X-rays and chemical substances

It is not known whether these factors cause malformations in man, but indirect evidence suggests that fœtal defects may sometimes be brought about by noxious agents or by an inadequate intrauterine environment Abnormal implantation of the ovum, as in tubal pregnancy, is associated with a high incidence of malformations (Mall 1908) The incidence is increased if bleeding has occurred in the early months of pregnancy (Burge 1951, Turnbull and Walker 1956) and in diabetic pregnancies (Peel and Oakley 1949) Gregg's (1941) observation is now generally accepted, that infection with rubella in early pregnancy is often followed by the birth of a deformed child

The incidence of congenital malformations is difficult to estimate The best study based on a defined population is that of Record and McKeown (1949) dealing with Birmingham Several reports based on hospital records are available, but, though the data are no doubt accurate, hospital patients are not necessarily representative of the population from which they are drawn National statistics refer only to deaths certified as due to deformity, and are by no means comprehensive Scottish vital statistics give much information about malformed stillbirths but very little about neonatal or infant deaths Those for England and Wales give no information about the causes of stillbirths and little about infant deaths due to malformations

This study deals with stillbirths and infant deaths associated with malformations The main group used for analysis consists of 37,585 single births to booked patients delivered in the Aberdeen Maternity Hospital in 1938–55 Lest the trends found were produced by selection of patients for hospital confinement, these were compared with those in all Aberdeen births in 1949–55 (Records for 1938–48 were not available on a city-wide basis) These local statistics are compared with certain national data derived from the annual reports of the Registrar-General for Scotland

Method

Group 1—The records of the Aberdeen Maternity Hospital for 1938–55 were searched for fœtal deformity in booked cases The present analysis has been restricted to cases of stillbirth or of infant death The records of infant deaths taking place some time after mother and child were discharged from hos-

TABLE I—DISTRIBUTION OF STILLBIRTHS AND INFANT DEATHS ASSOCIATED WITH CONGENITAL MALFORMATION, ACCORDING TO MATERNAL AGE AND PARITY

Expected numbers in parentheses, discrepancies in cross-totals are due to "rounding-off"
(Aberdeen Maternity Hospital booked cases, excluding twins and abortions, 1938–55)

Age (yr)	Anencephalus					Other malformations of C.N.S.					Other malformations				
	Parity				Total	Parity				Total	Parity				Total
	1st	2nd	3rd	4th+		1st	2nd	3rd	4th+		1st	2nd	3rd	4th+	
–19	9 (3 8)	(0 5)	(0 0)	(0 0)	9 (4 4)	12 (5 6)	1 (0 7)	(0 1)	(0 0)	13 (6·4)	3 (5 7)	1 (0 9)	(0 1)	(0·0)	4 (6 5)
20–24	22 (13·0)	6 (6·0)	1 (1 8)	(0 8)	29 (21 5)	26 (19 1)	9 (8 8)	4 (2 7)	(0 9)	39 (31 5)	20 (19 3)	9 (8 9)	6 (2 7)	2 (0 9)	37 (31 8)
25–29	6 (6 5)	6 (6 3)	1 (3 2)	2 (2 2)	15 (18 1)	8 (9 5)	6 (9 2)	2 (4 7)	3 (3 2)	19 (25 6)	14 (9 6)	5 (9 3)	4 (4 8)	3 (3 2)	26 (26 9)
30–34	1 (2 1)	1 (3 1)	1 (2 2)	1 (2 5)	4 (10 0)	3 (3 1)	1 (4 6)	4 (3 3)	3 (3 6)	11 (14 7)	(3 2)	1 (4 7)	2 (3 3)	2 (3 7)	5 (14 9)
35 or more	(0 9)	(1 3)	(1 2)	3 (2 6)	3 (6 0)	2 (1·4)	(1 9)	1 (1 7)	3 (3 8)	6 (8 9)	2 (1 4)	4 (1 9)	4 (1 8)	7 (3 8)	17 (9 0)
Total	38 (26·4)	13 (17 2)	3 (8 5)	6 (7 8)	60 (60 0)	51 (38 7)	17 (25 3)	11 (12 5)	9 (11 5)	88 (88 0)	39 (39 2)	20 (25 6)	16 (12 6)	14 (11 6)	89 (89 0)

pital are unavoidably incomplete, especially through emigration from the city, but this fact is unlikely to have introduced bias of any importance The data were analysed by age and parity

Group 2—Since 1949 punch-card records of all births in the city of Aberdeen have been maintained in the university department of midwifery, and those for 1949–55 have been used in this investigation to provide data referring to a defined population In addition to an analysis by age and parity the data were examined for primiparæ by social class and height

In groups 1 and 2 plural pregnancies were excluded to simplify analysis In group 2 the analysis was further restricted to legitimate births to patients resident in the city

Group 3—The annual reports of the Registrar General for Scotland (1939–55) provided data for stillbirths attributed to fœtal malformation, broken down by social class and by region Data by age and by parity (but not both together) are also available

Results

Incidence

Among the 37,585 single births in group 1 were 237 stillbirths and infant deaths attributable to congenital malformation (6 3 per 1000 births) These included 60 due to anencephalus (1 6 per 1000 births), 88 due to other deformities of the central nervous system (2 3 per 1000 births), and 89 to other malformations (2 4 per 1000 births), the equivalent rates on the basis of 20,961 city births (group 2) were 1 5, 1 8, and 2 2 respectively

It has been indicated above that these rates may be a little low owing to failure to identify all the infant deaths Fully comparable data are not easily extracted from national statistics In Scotland in 1939–55 the incidence of stillbirth certified as due to anencephalus was 2 7 per 1000, that of stillbirths plus first-year deaths due to malformations of the central nervous system was 3 7 per 1000, and those due to other types of malformations 3 9 per 1000 * These national rates are higher than those found for Aberdeen It will be shown below that the stillbirth-rates due to anencephalus in the city of Aberdeen are lower than those in the other large Scottish cities

Maternal Age and Parity

Table I gives the distribution by age and parity, in the Aberdeen Maternity Hospital group, of stillbirths and infant deaths due to the three groups of deformities distinguished above Closely comparable results were obtained in the smaller Aberdeen city group Since the numbers in several cells are very small, the calculation of rates is unprofitable, and instead the "expected numbers" in each age and parity group are shown, these have been calculated on the assumption that the cases of deformity were distributed in strict proportion to the total number of patients in each cell

Among the younger primiparæ the number of stillbirths and infant deaths due to anencephalus and other malformations of the central nervous system is more than twice the expected number No other notable excesses or deficits are evident On the other hand, in the group of "other malformations" the only clear excess is among mothers aged 35 or more The data show that much of the excess in the oldest age-group is attributable to mongolism (The deficit in the age-group 30–34 is believed to be due to chance)

Comparable national figures are unavailable The Registrar-General gives stillbirth-rates by age and by order of birth separately but does not give similar information for infant deaths The stillbirth-rates by age show relatively high incidences for anencephalus before the age of 20 and after that of 35, those for other malformations of the central nervous system and for "other malformations" are high only at the older ages Stillbirth-rates by birth order indicate an erratic increase with parity for anencephalus and other malformations of the central nervous system, there is no very definite trend by parity in the group "other malformations"

TABLE II—DISTRIBUTION OF STILLBIRTHS AND INFANT DEATHS DUE TO CONGENITAL MALFORMATION, BY MATERNAL HEIGHT AND SOCIAL CLASS

Expected numbers in parentheses, discrepancies in cross-totals are due to "rounding-off"
(City of Aberdeen, legitimate first single births 1949–55)

Height	Anencephalus				Other malformations of C.N.S.				Other malformations			
	Social class			Total	Social class			Total	Social class			Total
	I and II	III	IV and V		I and II	III	IV and V		I and II	III	IV and V	
5 ft. 4 in. or more	(1 1)	2 (2 9)	1 (0 9)	3 (4 9)	(1 2)	6 (3 2)	1 (1 0)	7 (5 5)	(1 2)	3 (3 1)	(0 9)	3 (5 2)
5 ft. 1 in.–5 ft. 3¾ in.	(1 1)	3 (5 1)	4 (2 1)	7 (8 3)	(1 2)	4 (5 7)	1 (2·4)	5 (9 3)	1 (1 1)	6 (5·4)	3 (2 3)	10 (8 8)
Less than 5 ft 1 in.	2 (0 2)	(2 3)	5 (1 2)	7 (3 8)	1 (0 3)	2 (2 6)	4 (1 3)	7 (4 2)	(0·3)	4 (2 5)	1 (1 3)	5 (4·0)
Total	2 (2·4)	5 (10·4)	10 (4 2)	17 (17·0)	1 (2 7)	12 (11 6)	6 (4 7)	19 (19 0)	1 (2·6)	13 (11 0)	4 (4 5)	18 (18·0)

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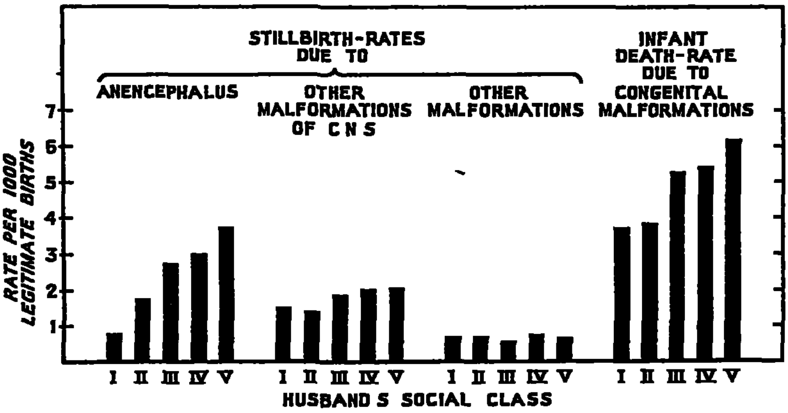
* The national rate for anencephalus is presumably reasonably accurate, since the condition is easy to diagnose and virtually all anencephalic babies are stillborn The rate cited here for other malformations of the central nervous system comprises stillbirths and infant deaths certified as due to hydrocephalus spina bifida, and ' other malformations of the central nervous system ' The group of ' other malformations ' (here assumed to exclude abnormalities of the central nervous system) includes deaths due to unspecified abnormalities, and ' monsters '



Incidence of stillbirths and infant deaths due to congenital malformations, according to social class (legitimate births, Scotland 1950-55)

Social Class and Height

In the data for 8245 married primiparæ resident and delivered in the city of Aberdeen in 1949–55 the social class and height were both specified in 8221 records Table II gives the distribution of stillbirths and infant deaths in the three ætiological groups previously distinguished, together with the numbers expected Although the numbers are small, there is clearly an excess of anencephalus and, to a lesser extent, of malformations of the central nervous system in the lower social classes and in small women These trends do not appear in the group " other malformations "

The Registrar General for Scotland has, since 1950, published data relating to legitimate stillbirths due to congenital deformities Fig 1 shows that, as social status falls, there is a steady increase in the incidence of anencephalic stillbirths There is a smaller, but similar, social-class trend in stillbirth-rates due to other malformations of the central nervous system but none in stillbirths from " other malformations " Infant deaths due to " congenital malformation " also show an increase in rate as social class falls, but unfortunately these deaths cannot be subdivided into specific ætiological groups

Geographical Differences

In 1950-55 there were 2919 stillbirths certified as due to congenital malformations among 563,863 births in Scotland—a rate of 5 17 per 1000 births The distribution of these according to place of birth showed that the highest incidence was in central and southern Scotland, followed by the north-eastern counties, with the lowest incidence in the crofting counties in the north and west. These differences were due largely to variations in the incidence of anencephalic stillbirths, the incidence of which was as follows

Crofting counties of North and West Scotland (Orkney, Shetland, Caithness, Sutherland, Ross and Cromarty, Inverness, Argyll, Bute)	1 29 per 1000 births
Mainly agricultural counties, central and north-east (Perth, Nairn, Moray, Banff, Aberdeen, Kincardine, Angus)	2 15 per 1000 births
Agricultural counties of south, with scattered industrial areas (Ayr, Wigton, Kirkcudbright Dumfries, Peebles Selkirk, Roxburgh, Berwick)	2 65 per 1000 births
Central counties, mainly industrial (Dunbarton, Clackmannan, Kinross, Fife, Lanark, Renfrew, Mid-, West, and East Lothian, Stirling)	2 95 per 1000 births

The incidence per 1000 births of anencephalic stillbirths in the four large cities of Scotland was Aberdeen, 1 7, Edinburgh, 2 5, Dundee, 2 9, Glasgow, 3 1 The order is that which might be expected from a knowledge of the social history of each city, on the assumption that poor social conditions predispose to anencephalus

Conclusions

The literature on the effects of age, parity, social class, and other factors on the incidence of fœtal malformations of various kinds is fairly extensive, but there is much disagreement, and few trends seem to have achieved general acceptance The facts given here suggest that primigravidæ living in poor social circumstances, particularly in industrial communities, have a higher risk than any other group of pregnant women of fœtal death due to malformation of the central nervous system

These facts are as follows

(1) The geographical distribution in Scotland of stillbirths due to malformations of the central nervous system, especially anencephalus, shows the highest rates in the central industrial belt, and the lowest rates in the crofting counties of the west These differences are unlikely to be due to differences of certification, and do not obtain in stillbirth-rates due to malformations other than those of the central nervous system

(2) National statistics—available for women of all parities—show a distinct social-class gradient in stillbirths due to anencephalus, there is a *less steep gradient in stillbirths due* to other malformations of the central nervous system, and none in those due to " other malformations "

(3) Aberdeen data point to a relatively high incidence of anencephalus and other malformations of the central nervous system in young primigravidæ, especially those aged less than 20 *Very few of such young primigravidæ* come from the upper social classes

(4) Closer examination of the Aberdeen cases, which are too few to admit of definite conclusions being drawn, indicates that, within social classes IV and V, it is those undersized women, stunted by the environment in which they have grown, who have the highest incidence of stillbirth and infant death due to malformation of the central nervous system

It is unprofitable, on present evidence, to speculate too far on the nature of possible environmental causes of congenital malformations, especially of the central nervous system Several factors might act together or separately, and different factors may produce the same end-results by interfering with one specific phase of organogenesis Nor should it be inferred from our data that environmental influences are necessarily major " causes " of malformations of the central nervous system, at most, such influences probably act by bringing out latent tendencies The genetics of anencephalus have been discussed comprehensively by Penrose (1957)

One final point may be made the hypothetical environmental influences need not necessarily be present for the first time during early pregnancy For example, if a poor diet is regarded as a possible predisposing factor, chronic malnutrition during growth and adolescence may be as significant as an inadequate diet during early pregnancy Prevention is likely to depend on long-term general measures which will secure high standards of growth and health Measures aimed specifically at improving the diet and health of mothers during the first four weeks of pregnancy, by the end of which time the neural canal of the embryo has closed, are obviously impracticable

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LEIOMYOMA OF STOMACH

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THE estimated incidence of gastric leiomyoma varies greatly Meissner (1944) found twenty-three affected stomachs (eleven with multiple tumours) in fifty random necropsies, and Riemets (1930) thirty-two affected stomachs in two hundred consecutive necropsies Many of these tumours were but a few millimetres in diameter Clinically significant tumours are much less common Marshall (1955) states that 4 8% of gastric tumours are benign, while Minnes and Geschickter (1936) estimated that leiomyomata form 36% of benign gastric tumours and are the commonest type of benign new growth of the stomach Thus it would seem that leiomyomata may account for about 2% of all gastric tumours This agrees with Cowdell's (1950) estimate of 2 4% but is much higher than the estimate of 1 in 2000 given by Ingram and Johnson (1956), whose figure probably more closely corresponds to common experience

The present case is reported because of the long period of preoperative observation, the confusion of the gastric mass with the spleen, and the success of surgery in a patient aged 84

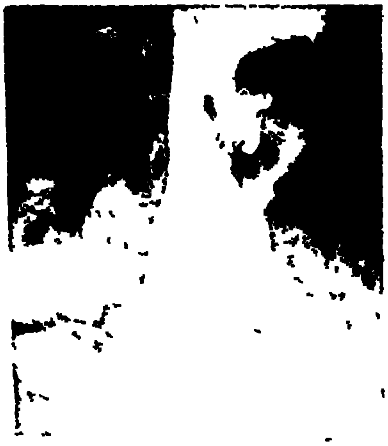

Fig 1—Large ulcerated filling defect arising from the greater curvature

Case-report

A woman, aged 78, was first seen in October, 1950, with a history of having vomited much blood ten days earlier, followed by the passage of black tarry stools For the previous few months she had felt vaguely unwell with upper abdominal discomfort, which was slightly relieved by alkalis She stated that three and a quarter years before this admission she had begun to feel tired and faint and was treated by her doctor for anæmia On admission she was alert but very pale The only significant finding was a mass situated in her left hypochondrium, measuring about 5 in. by 3 in, and resembling an enlarged spleen Her hæmoglobin was 40% She was treated by blood-transfusion and with ferrous sulphate by mouth, and on discharge her hæmoglobin was 88% Biopsy of her sternal marrow showed that it was hyperplastic, with active erythropoiesis of normochromic type Liver-function tests, bleeding-time, and clotting-time were normal A barium meal showed no gastric or œsophageal varices but showed mild pseudo-hypertrophic gastritis No gastric ulcer or neoplasm was seen, and the duodenal cap appeared normal

The patient remained well for a year and then had a slight melæna Two years after this (in October, 1953) she was readmitted with increasing listlessness, tiredness, and further melæna On examination the same mass was felt and the hæmoglobin was 42% Again the patient was transfused and given oral iron, her hæmoglobin being brought up to 83% before discharge Thereafter she remained very well until August, 1957, when she was readmitted complaining of two days' faintness and passing tarry stools She had had a small hæmatemesis three months before

On admission the only significant finding was the mass situated below her left costal margin and extending almost to her umbilicus There was no clinical evidence of portal hypertension or of hepatic failure Her hæmoglobin was 38%, and a blood-transfusion was given, eight pints being required to increase her hæmoglobin to 81%

Further treatment and progress—When the patient's condition had sufficiently improved, liver-function tests were done and showed serum-bilirubin, direct 0 1 mg per 100 ml, indirect 0 4 mg per 100 ml, total 0 5 mg per 100 ml, serum-alkaline phosphatase 6 King-Armstrong units, thymol turbidity 1 unit, thymol flocculation 0 unit, serum-colloidal gold 0 unit, zinc-sulphate turbidity 4 units, ammonium-sulphate turbidity 1 unit The episodes of bleeding were thought to be due to œsophageal varices in association with portal hypertension, the mass in the left hypochondrium being regarded as splenic A barium swallow and meal showed that the œsophagus was normal However, a large ulcerated filling defect arising from the greater curvature of the stomach was seen (fig 1)

Laparotomy (Mr Harold Edwards) revealed a hard irregular growth on the anterior wall of the stomach There were enlarged lymph-nodes in the omentum, but the liver contained no metastases A second pale yellow subserous tumour, 2 cm in diameter, was seen on the anterior wall of the stomach 5 cm above the larger mass A sleeve resection of the stomach was done, the mass being removed entire Postoperative progress was satisfactory, and on discharge the patient's hæmoglobin was 96%

Pathological report (Dr J H O Earle)—The operation specimen was part of the stomach wall and measured 13 cm × 8 cm, with a central protuberant area 5 5 cm in diameter with central ulceration (fig 2) This was continuous with the tumour (10 5 cm × 12 cm × 8 cm) outside the stomach wall On section the tumour was seen infiltrating between the mucosa and the serosa Centrally it infiltrated directly through the serosa to spread as a large extragastric mass The tumour appeared grey-white flecked with yellowish areas of necrosis and areas of hæmorrhage Microscopy showed a leiomyoma with areas of degeneration and hæmorrhage No invasion of lymph-nodes was found The relative absence of mitoses and the mature type of muscle-cell indicated that the tumour was benign

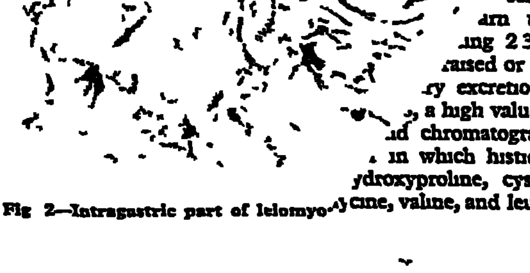

Fig 2—Intragastric part of leiomyo-

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Discussion

Leiomyomata usually give rise to symptoms in the older age-groups, 75% in the fifth to seventh decades (Baker and Good 1955) In fifty-one cases reported with clinical details (Christensen 1957, Cowdell 1950, Davis and Adams 1956, Down 1930, Golden and Stout 1941, Harris 1957, Lund 1955, Marshall and Cherry 1955, Morrin 1956) bleeding was the commonest presentation (74%) and was more often severe and acute than occult Abdominal pain occurred in 69%, and a mass was felt in 40%, in one case the mass was confused with the spleen Other clinical manifestations include pyloric obstruction, volvulus of the stomach (Ker 1955), and perforation and bleeding into the peritoneum (Cowdell 1950, Millar 1928) Most cases present after a very short history, but where pain predominates the history may be long, in one there was a seven-year history and a barium meal showed displacement of the stomach six years before operation (Ker 1955) Another patient gave a fifteen-year history (Davis and Adams 1956) In no case has a recurrence been reported, even in cases followed for thirteen years (Morton, et al 1956) and seventeen years (Harris 1957)

This description underlines the essentially benign nature of most of these tumours Malignant deterioration is said to occur, but even histologically malignancy is difficult to determine (Golden and Stout 1941) and is best assessed by the frequency of mitotic figures (Lumb 1951) Death from hæmorrhage is a greater danger than malignancy, so resection is strongly indicated The frequency of massive hæmorrhage and the absence of cachexia in the presence of an abdominal mass distinguish leiomyoma from carcinoma of the stomach

Radiological abnormalities occur in the large majority of gastric leiomyomata (Baker and Good 1955), and the benign nature of the growth may be suggested by the radiological picture A subserous tumour may be visible as a soft-tissue shadow on straight radiography (Davis and Adams 1956) and may displace surrounding viscera, it may distort the barium-filled stomach by traction, or by pressure appear as an extrinsic mass distorting the mucosal folds (Baker and Good 1956)

A submucous tumour may produce a punched-out filling defect of the barium-filled stomach, usually arising from the gastric wall and leaving the curvatures regular The rugæ are obliterated in the immediate region of the tumour but around it appear normal in distribution and arrangement The tumour does not disturb peristalsis or cause spasm (Moore 1924) When ulceration takes place, the mucosal folds do not converge on the crater (Abrams 1954)

Summary

A gastric leiomyoma was present for ten years before operation at the age of 84

The principal features were repeated hæmorrhage and a palpable mass closely resembling an enlarged spleen

A normal barium meal initially led to the diagnosis of splenic anæmia and œsophageal varices

Seven years later the barium meal was grossly abnormal

Successful removal [illegible] tumour led to complete recovery

I wish to thank Dr T C whose care this patient was ad for his help an for the and gastrecto

at foot

ACCIDENTAL POISONING IN CHILDHOOD

AN EXPERIMENTAL APPROACH TO THE PREVENTION OF POISONING BY TABLETS

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T R W Forrest
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Young children are often poisoned through swallowing drugs in tablet form which have been prescribed for adults, and it has been felt that the attractive appearance of these tablets is one factor in the problem An experiment was therefore carried out to determine the frequency with which different colours were chosen by children when offered a selection of ten coloured tablets By this means it was hoped to determine which colours were least popular among children and might therefore be most suitable for adult tablets

Method

The children tested ranged in age from 1 to 8 years Below the age of 1 the child tended to take more than one tablet, and his grasp was insufficiently accurate to allow of an assessment as to which was his primary choice The same was true of some of those over 1 year of age, in which case the child was not included in the study Those over 8 years were not included, since they were regarded as being beyond the age at risk The children tested were inpatients, outpatients, and those attending for school medical examinations Each child was offered a plate on which were ten lactose tablets coated in the following colours blue, black, brown, orange, white, yellow, pink, green, wine, and magenta For each child the plate was shaken and turned round to reduce any error from the child choosing the nearest tablet Similarly, to obviate any personal bias in the adult making the test, a number of different testers were employed

No attempt was made to introduce the question of different tastes into the test It has been suggested that bitter tablets would be less often accidentally swallowed by children, but many of the poisons taken in this way do taste unpleasant, so it seems that the child can swallow a handful before he appreciates the unpleasant taste

Results

613 children were tested, of whom 316 were boys and 297 girls Age did not appear to be significant in relation to the colour chosen but the ages of the children were

Age (yr)	*No of children tested*	*Age (yr)*	*No of children tested*
1	22	5	163
2	70	6	42
3	46	7	176
4	70	8	24

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The results, in order of preference, were

NO OF TABLETS SELECTED

Colour	Boys	Girls	Total
Magenta	52	52	104
Pink	39	35	74
Blue	25	41	66
Orange	33	31	64
Brown	36	25	61
Yellow	30	26	56
White	30	22	52
Green	21	26	47
Black	25	20	45
Wine	25	19	44

Discussion

These results show the bright colours to be the most popular, with magenta an easy winner Brown, a dull colour, is relatively high on the list, presumably because of its similarity to chocolate Wine and black are understandably found at the lower end of the list, though green's low placing was surprising

The results suggest the use of black tablets, but these have the disadvantage that, if spilt on the floor, they would not so easily be seen and might later be picked up by children It is significant that white, though a bright colour, was not in the popular range, and we think this may be because the children believed that the white one was a "pill" and not a sweet In view of these results, and particularly if this argument is valid, it would seem wiser for tablets to be kept white in order that they should look like "pills", rather than that attractive colours should be introduced which make them look like sweets To achieve this it is not only a matter of persuading the chemist to manufacture white tablets, but of educating doctors and patients to accept only such tablets Robinson (1956) pointed out that his firm (Evans Medical Supplies) had produced a white form of tab ferr sulph, but that these were not wanted and that the demand was for coloured tablets

Against the use of white tablets it might be argued that aspirins are of this colour and yet often poison children It is felt, however, that this is because aspirins are the commonest household tablet

Finally it must be emphasised that the choice of a suitable colour is only one of the means of lowering the rate of accidental poisoning by tablets Ideally (Jolly 1956) all poisonous tablets should be dispensed in 'Cellophane' strips which are difficult for the child to undo and make him more likely to take only one tablet at a time Unfortunately, the present competitive prices make such expensive packing impracticable for the manufacturer unless a policy could be agreed by all manufacturers

The only real safeguard is for all tablets to be kept in locked containers

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Addendum

Since this paper was written Grainger (1958) has reported an experiment using different coloured sweets He came to the conclusion that children preferred the coloured to the white ones, but his experimental method was open to criticism, and this was raised by correspondents in the following two numbers of the same journal

We are indebted to Glaxo Laboratories Ltd for the coloured tablets

ACUTE CASE OF WILSON'S DISEASE

(HEPATOLENTICULAR DEGENERATION)

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IT is now generally realised that hepatolenticular degeneration varies greatly in its speed of progression (Wilson 1912, Hall 1921, Raskin and Mackenzie 1956, Walshe 1956a, Bearn 1956) and in the relative prominence of neurological and hepatic symptoms (Bickel et al 1955)

Walshe (1957) has reviewed Wilson's disease with particular reference to the biochemical lesion and has critically discussed the current theories of the pathogenesis of this disease

The great majority of reports of the treatment of this condition are confined to the more chronic neurological cases Acute cases seem to be altogether less common, but this may only reflect the greater difficulty in recognising the syndrome We therefore report here the course of such an illness

Case-report

A boy, aged 12 years, was admitted to Addenbrooke's Hospital on Dec 29, 1955, with two weeks' history of malaise and anorexia He had pain in both knees, and his parents said that his legs were swollen Up to the time of this illness he had apparently been in good health

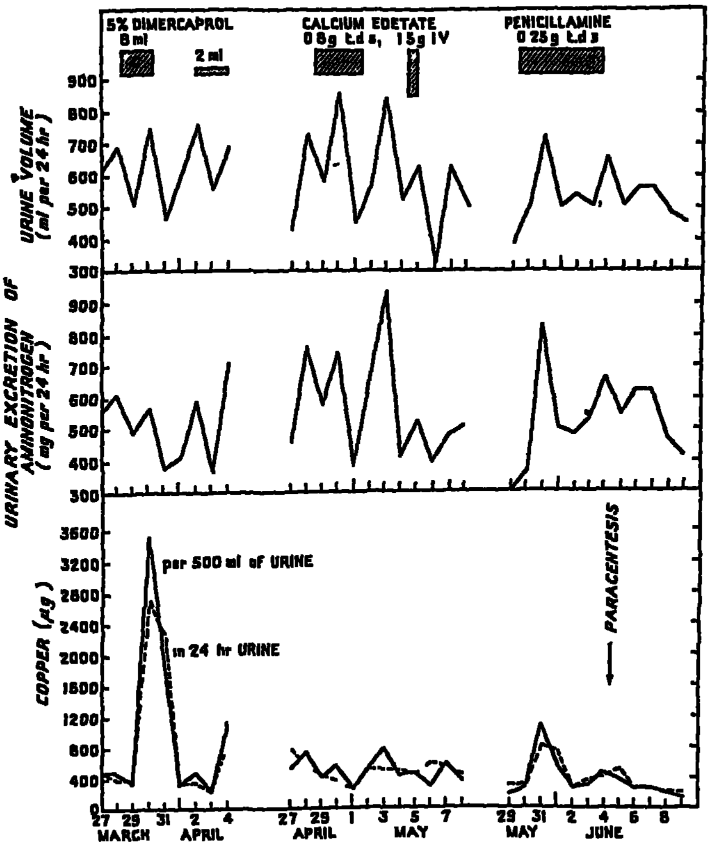
Family history—His parents are first cousins and both are healthy, as are his two surviving brothers A brother who died at the age of 18 was reported to have had "paralysis" for four or five years after a head injury of unknown severity and finally to have died with "fits" Inquiry has not thrown any further light on this illness, it may be compatible with a diagnosis of Wilson's disease but it is not conclusive

On examination the patient was pale, ill, and apprehensive, and did not speak or smile He had conspicuous œdema of his legs and sacrum, and considerable abdominal distension, with much free fluid in the abdominal cavity His liver and spleen could not be felt Signs of a moderate pleural effusion were present at the base of his right lung

Investigations—Radiography revealed œsophageal varices and probably gastric varices also The serum-protein level was 6 0 g per 100 ml, and paper electrophoresis showed an extreme deficiency of albumin and a considerable excess of γ-globulin The serum-bilirubin level was 0 6 mg per 100 ml, serum-cholesterol 200 mg per 100 ml, and serum-uric acid 2 0 mg per 100 ml The thymol flocculation test was negative, thymol turbidity 10 units, and alkaline phosphatase 7 8 Bodansky units The prothrombin content of the plasma was 21% of the average normal by Quick's one-stage method Symptomatic treatment for eight weeks having produced little clinical improvement, the patient's urine was collected for twenty-four hours with due precautions against contamination by copper This contained 166 μg of copper, an abnormally high value but not above the figures cited for some adult cases of cirrhosis, not clinically Wilson's disease, by Cartwright et al (1954) and Bearn and Kunkel (1954) However, the serum-paraphenylenediamine-oxidase activity was 2 Bearn units (Bearn and Kunkel 1954), the normal range being 2 3–5 2 units, and cases of ordinary cirrhosis showing a raised or high normal activity (3 5–13 2 units) The urinary excretion of aminoacids was 0 47 g per twenty-four hours, a high value for a child aged 12 years, electrophoresis and chromatography revealed an unusual aminoacid pattern in which histidine, tryptophane, lysine, aspartic acid, hydroxyproline, cystine, methionine, alanine, phenylalanine, glycine, valine, and leucine were increased in amount, and threonine and citrulline were present in conspicuous amounts (Taurine was present in normal amounts)

Diagnosis and treatment —On these findings Wilson's disease was diagnosed, and therapy with dimercaprol was begun During the second course of this treatment the patient's daily output of urine decreased to 35 ml , and dimercaprol was withheld at once No other toxic effects were noted No clinical benefit was observed from this limited period of treatment, but much more copper was excreted (see figure) After four weeks' rest, in which no clinical change was observed, treatment with calcium edetate was followed by a slight increase in the output of copper After four weeks penicillamine was given (Walshe 1956a and b) The initial increase in excretion of copper was poorly maintained, and the child, now severely ill, showed no improvement The urinary output of aminoacids, unchanged by treatment with either dimercaprol or calcium edetate, increased during, and for some time after, penicillamine therapy, probably because penicillamine is an aminoacid which is excreted largely unchanged During this period an extra band, having the same mobility as penicillamine, appeared in electrophoretic separations of urinary aminoacids

Course —During the five months' treatment in the ward this child had remained uncommunicative, with conspicuous lack of facial expression, indicating profound emotional disturbance. He was apt with his hands and fully aware of what went on in the ward When interfered with, he was liable to outbursts of fighting and screaming However, none of the neurological findings more usually associated with Wilson's disease were in evidence Tremor was never detected He developed spider nævi on his hands and face and conspicuous gynæcomastia Kayser-Fleischer rings, hardly visible at first to the naked eye, were clearly seen on slit-lamp examination A mild diplopia was also detected Paracentesis was done for ascites on three occasions On June 18, 1956, the boy lapsed into coma and died Details of treatment and of urinary excretion of copper and aminoacids are given in the accompanying figure



Treatment and urinary excretion of copper and aminoacids

Necropsy findings —The body was that of a wasted male child weighing 39 kg , with ascites and with pitting œdema of the ankles and thighs The liver was small (985 g), studded with yellowish nodules up to 0 6 cm in diameter The cut surface showed nodules throughout the substance of both lobes The spleen was enlarged (625 g) and had a firm solid pulp Œsophageal varices were present The outer and cut surfaces of the brain revealed no obvious abnormality, and no cavitation was seen in the basal ganglia

Microscopy —The liver showed severe fibrosis with regeneration nodules, some cells showing recent acute degeneration, and there was conspicuous infiltration with chronic inflammatory cells The picture resembled subacute hepatitis with continuing necrosis The basal ganglia showed a probable loss of neurones and an increase in glia, with pallidal siderosis, and fibrillar structures, probably microglial processes, which stained strongly with stains for copper No abnormality was seen in any other section of the central nervous system In the cornea pigment granules, histochemically containing copper, were seen in the membrane of Descemet, towards the limbus, confirming the presence of the Kayser-Fleischer rings Apart from the Kayser-Fleischer rings the histological findings were not specific for Wilson's disease, but the presence of much copper in the tissues was demonstrated both histochemically and by bulk analysis The histochemical techniques are described in the appendix (see below)

Discussion

The unusual features of this case are as follows

(1) *The absence of tremor and neurological signs* —The emotional behaviour, expressionless face, and paucity of speech were probably facets of the disturbance in Wilson's disease, but they are in themselves too indefinite to be regarded as signs of involvement of the central nervous system

(2) *The absence of diagnostic pathology in the basal ganglia* —Such cases have been reported before (e g , Raskin and MacKenzie [1955]) and some of the changes in the ganglia (e g , the copper-positive glial fibres) may be more specific than we at present realise

(3) *The short duration of the illness* —Several such cases have been published since the original description of Ormerod's case (Wilson 1912)

It therefore seems that this is a true case of Wilson's disease in which the liver dysfunction has dominated the clinical picture, and the disease has been so acute that the changes in the basal ganglia have not had time to reach cavitation before death This case is similar to case 12 described by Bickel et al (1957), who also describe two cases similar to the present case in that the Kayser-Fleischer rings were only discernible on slit-lamp examination Chalmers et al (1957) describe five cases of an " abdominal " form of Wilson's disease in which there were no significant neurological findings, and there seems to be little doubt that the present case belongs to this group

In the present case, of the three agents at present available for therapy, dimercaprol seemed to be the most effective, but it necessitated frequent painful intramuscular injections, it is also very toxic and must be used with caution Calcium edetate appeared to be relatively ineffective and, in view of the trouble of intravenous infusions, is clearly unsuitable for long term therapy

Penicillamine may offer a good alternative to dimercaprol, especially where injections at short intervals are impracticable. Walshe (1956a) and Osborn and Walshe (1958) compare it very favourably with dimercaprol Our findings as regards the relative efficacy of dimercaprol, calcium edetate, and penicillamine in promoting urinary excretion of copper are most unusual The case, however, was of a very exceptional type, and the disease was nearing a fatal termination when calcium edetate and penicillamine were tried Intravenous infusions of coeruloplasmin have been tried (Bickel et al 1957), but their clinical value is not yet clear

Summary

An acute case of Wilson's disease is described, together with the necropsy findings Minimal involvement of the central nervous system was associated with an excessive urinary excretion of copper and aminoacids, and a low serum-paraphenylenediamine-oxidase activity Treatment with dimercaprol greatly increased the copper output, calcium edetate and penicillamine being less effective.

We wish to thank Dr D Gairdner and Dr J D Roscoe for permission to publish and for advice on the presentation of the clinical material, Dr A M Barrett for his help with the histology, Mr G C Spurgeon for technical assistance in the preparation of the histological material, and the Distillers' Co Ltd for a gift of penicillamine

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Appendix

Methods

Copper was estimated by a slight modification of the method of Eden and Green (1940), with due care to avoid contamination We obtained duplication of analyses within ±4% of their mean, and a reagent blank of not more than 1 μg of copper

Cœruloplasmin was estimated by the method cited by Bearn and Kunkel (1954)

Total aminonitrogen was determined by the method of Albanese and Irby (1944) Urinary aminoacids were studied by zone electrophoresis and by two-dimensional chromotography

Material for histochemical study was fixed in neutral buffered formol saline (pH=7·0), prepared with analar reagents, and containing 31μg of copper per litre The hæmatoxylin technique of Mallory and Parker (1931) was used to search for excessive copper, since this technique is of rather doubtful specificity, positive material was then stained with 0·5% rubeanic acid in ethanol and with 1% dithiosemicarbazone in citric-acid solution Positive reactions with all three stains were obtained in liver, cornea, and basal ganglia.

"Dr Betts found when he visited patients, that when he seemed to be in great haste, they used to detain him long upon some frivolous questions, and when he took no great notice but began to ask questions himself, they never endeavoured to stay him, by which practice his visits were but short, wherever he came"—Journal-Book of the Royal Society for June 19, 1700 *Notes and Records of the Royal Society of London*, 1951, 8, 157

POPLITEAL EMBOLECTOMY
WITH RETROGRADE FLUSHING VIA THE POSTERIOR TIBIAL ARTERY

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The conservative approach to the treatment of peripheral arterial embolism has inherent limitations For instance, such treatment is usually deemed successful if the limb is saved, though generally under such circumstances residual ischæmic symptoms persist and may be severe On the other hand, successful embolectomy has a more satisfactory end-result, as the limb is returned to normal When embolectomy is unsuccessful it is usually because it is undertaken too late, after distal arterial thrombosis has begun, aided perhaps by fragmentation of the embolus Under these conditions Shaw (1956) has shown that a more aggressive surgical approach is necessary This entails opening the artery distally and flushing it out retrogradely with heparin in saline solution

I here report a case of popliteal-artery embolism with distal thrombosis which was successfully treated in this manner

Case-report

A man, aged 51, entered hospital because of severe pain, of seven hours' duration, in the left popliteal fossa The pain was of sudden onset, and spread to become generalised over the upper calf He noted intense pallor, coldness, and numbness of his foot He could not walk and latterly had had some difficulty moving his toes He had had atrial fibrillation, complicating rheumatic heart-disease, for several years

Examination—His pulse was irregular (rate 96 a minute), and blood-pressure 150/78 mm Hg A systolic murmur was present over the cardiac apex The left leg was cold and cyanotic from midcalf level, with diminished sensation over this area Although active movements of the toes and ankle were possible, weakness was obvious, both of dorsiflexion and plantarflexion The left femoral and popliteal pulses were easily palpated, but both anterior and posterior tibial pulses were absent On the right side the peripheral pulses were present

Treatment—Anticoagulant therapy was begun and peripheral vasodilatation encouraged by sedation, the administration of whisky, and heating the trunk and hands After three hours there was no improvement in the condition of the left leg, the skin temperature fell 5°C during this period. Operation was undertaken

Operation—Under general anæsthesia the left popliteal artery was exposed and opened about 2 inches above its bifurcation. Good bleeding was obtained from the proximal end but none from the distal end Suction via polyethylene tubing was without effect The posterior tibial artery was then exposed at the ankle and opened No clot was present By use of a 50 ml syringe, retrograde flushing was carried out with heparin in physiological saline solution (10,000 units heparin per 500 ml) Small fragments of clot escaped via the popliteal arteriotomy 300 ml of solution was used. Both arterial incisions were then closed Before skin closure, no pulse was palpated in the posterior tibial artery At the end of operation the condition of the leg had greatly improved. There was no

Arteriogram ten weeks after embolectomy, showing patent popliteal and proximal anterior and posterior tibial arteries cyanosis or pallor, the foot and toes being of good colour Neither anterior nor posterior tibial artery could be palpated

Postoperative progress —The condition of the patient's foot remained satisfactory, and the posterior tibial pulse was palpable on the seventh postoperative day, but some weakness of dorsiflexion of the foot persisted Anticoagulant therapy was begun on the seventh postoperative day, and was continued for two months An arteriogram ten weeks after operation showed that the popliteal and posterior tibial arteries were patent (see fig 1) The anterior tibial artery was blocked about midcalf level Six months after operation weakness of dorsiflexion persisted There were no other complaints

It seems likely that the return of an adequate peripheral circulation was due to the retrograde flushing with removal of fragments of embolus and propagated thrombus from the posterial tibial artery The persistent weakness of dorsiflexion of the ankle may have resulted from damage to the lateral popliteal nerve during operation or may have been the result of ischæmia The former was not considered likely since the nerve in question was neither stretched nor damaged at operation The possibility of ischæmic damage was suggested by the postoperative arteriographic findings This underlined the need for retrograde flushing of the anterior as well as the posterior tibial artery in similar circumstances

Discussion

The exact place of surgery in the treatment of peripheral arterial embolism is a matter of some dispute The advent of the anticoagulant drugs laid emphasis on the conservative approach, which was furthermore often held justified because of the poor results of late surgery—notwithstanding the knowledge that the results of surgery were better the earlier embolectomy was undertaken It is wise in early cases to initiate conservative measures, but these must be abandoned for surgery if after two to three hours the peripheral circulation has failed to improve In late cases there is the added possibility of the presence of distal propagated thrombus, and indeed the likely presence of such clot has been regarded as justifying a refusal to operate

It is now apparent that by means of retrograde flushing some cases may be retrieved after the lapse of over twenty-four hours from the onset of ischæmia, and even where gross ischæmic changes, such as anæsthesia and complete loss of power, are present (Shaw 1956) This procedure was first described by Lerman et al (1930), and was revived by Shaw and by Crawford and DeBakey (1956) Shaw has applied it with success in late cases of acute thrombosis as well as embolism, in one instance thirty-three hours after the onset of severe ischæmic changes in the limb

With few exceptions only surgery can restore the limb to normal in cases of acute arterial insufficiency due to embolism or thrombosis, and, even after delay has led to considerable deterioration in the limb, operation may still restore the peripheral circulation

Summary

A case of embolism of the popliteal artery was treated by popliteal and posterior-tibial arteriotomies with retrograde flushing to remove emboli and propagated thrombus

Adequate circulation was restored

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Medical Societies

AMERICAN GASTROENTEROLOGICAL ASSOCIATION

THE Association's 59th annual meeting was held, under the chairmanship of Dr **CLIFFORD J BARBORKA** (Chicago, Ill), at Washington on May 30 and 31

Bilirubin Metabolism

Dr **RUDI SCHMID** (Boston, Mass) traced bilirubin production from the breakdown of a red blood-cell at the end of its 120-day lifespan The protoporphyrin ring is broken open to yield biliverdin, and this in turn yields free bilirubin, which is insoluble Solubility is achieved after passage through the liver, which conjugates one molecule of the compound with two molecules of glucuronic acid The insolubility of the free form and the solubility of the diglucuronide form of bilirubin account for the indirect and direct van den Bergh reactions The insoluble free form cannot be excreted by the kidney, hence in hæmolytic anæmias jaundice is acholuric since only the free form is present in excess Congenital non-hæmolytic jaundice is due to an intrahepatic enzymatic defect causing failure of conjugation of free bilirubin with glucuronic acid, as can be demonstrated in a strain of rats subject to this defect Jaundice of the newborn may be due to delay in development of the same mechanism

Dr **IRWIN M ARIAS** (New York) outlined the enzyme system responsible for the conjugation of bilirubin within the liver Glucuronic acid is mobilised by a transferase from uridine diphosphate glucuronic acid (U D P G A) This system has many applications, it is the method of transporting and excreting salicylates, which patients with the rare congenital condition of non-hæmolytic jaundice cannot metabolise

Dr **KURT ISSELBACHER** (Boston, Mass) pointed out that the U D P G A transferase system has many purposes either for detoxification by rendering substances physiologically inactive, or for making substances soluble, the corticosteroids, the sex hormones, thyroxine, morphine, and adrenaline are metabolised by the system—and serotonin to a lesser extent Glucuronide is formed from glycogen and glucose and becomes attached to uridine diphosphate

Dr **JESSE L BOLLMAN** (Rochester, Minn) referred to the monoglucuronide form of bilirubin which is found in the serum of dogs after removal of the liver when the diglucuronide is of necessity absent After experimental damage to the liver following administration of carbon tetrachloride, diglucuronide is much reduced and monoglucuronide proportionally increased The ratio of the di- to the mono- form—normally 3 to 1—may provide a basis for a diagnostic test in cases of jaundice In obstructive jaundice liver cells still function and an abnormally high proportion of diglucuronide can be demonstrated, whereas in hepatitis the proportion of diglucuronide is abnormally low In chlorpromazine jaundice there is a preponderance of monoglucuronide, suggesting hepatocellular damage rather than obstruction due to œdema of the intrahepatic ducts The presence of monoglucuronide after liver extirpation in dogs seems to suggest an extrahepatic site of conjugation

Assessment of Liver Function

Dr **NORBERT HENNING** (Erlangen, Germany) assesses portal circulation-times by duodenal instillation either of an acetylene derivative from which acetylene is metabolised by the liver and excreted from the lungs and can then be estimated in the expired air, or of ^{131}I, the rate of decrease in radioactivity over the duodenum then being determined An increased portal pressure can be revealed by the pressure at which rectal mucosa blanches on direct contact through a sigmoidoscope Alternatively the amount of heat which may be reabsorbed through a thermocouple in contact with colonic mucosa from a source of heat applied to the mucosa at a point nearby is directly proportional to the portal flow

Dr E Englert (Boston, Mass) has been using radioactive rose-bengal to study uptake in liver from the blood, liver storage, and excretion

Dr E Pineda (Boston, Mass) showed how the enzyme β-glucuronidase in the serum increases in hepatitis and falls below normal levels in liver failure, while Dr K S Henley (Ann Arbor, Michigan) has devised a technique for studying liver parenchymatous cells alone to the exclusion of the Kupfer cells and thus the enzymes glutamic oxalacetic transaminase and glutamic pyruvic transaminase, his work indicates that G P T is a more sensitive guide to hepatic dysfunction than is G O T

Dr F Wroblewski (New York) observed that changes of enzyme level in the serum do not reflect liver necrosis, nor liver function generally

Dr G Jerzy Glass (New York), using radioactive vitamin B_{12}, has shown that the greatest bodily store of this vitamin is in the liver, where the substance is in greater concentration than elsewhere, vitamin B_{12} is stored to a far lesser extent in the kidneys

The Pancreas

Opening a symposium in memory of the late Dr Mandred W Comfort, Dr Paul Nemir (Philadelphia, Pa) said that he has found that interstitial non-lethal pancreatitis follows the experimental intraperitoneal injection of activated pancreatic juice obtained from an isolated jejunal loop, it also follows injection of mixtures of pancreatic juice and organisms such as *Clostridium welchii* and *Escherichia coli* By contrast, activated pancreatic juice mixed with blood is highly toxic, and on injection causes lethal acute necrotising pancreatitis From this Dr Nemir inferred that in man pancreatitis becomes severe when vascular damage to the gland permits the escape of blood which then comes into contact with the enzymatic action of the liberated pancreatic juices

Dr Henry Janowitz (New York) has found that the trans-sphincteric rate of flow of pancreatic juice following secretin injection in patients with chronic pancreatitis, half of whom had radiological evidence of calcification in the gland, was not substantially less than in a control group of patients There was therefore little evidence to indicate ductal obstruction Dr Morton Grossman (Los Angeles, Cal) challenged this conclusion, since partial obstruction has been shown physiologically not to decrease but rather to increase the rate of flow

Dr John Budd (St Louis, Missouri) compared the urinary-diastase and serum-amylase levels in different pancreatic conditions Though in acute pancreatitis there is parallelism between the two initially, the diastase in urine remains increased longer, so this test may be used as an indication of persistence of the disease In hæmorrhagic disease, only the urinary diastase may be affected—and that at a later stage Estimation of urinary diastase has a place, therefore, as a clinical test in pancreatic disease

Gastrointestinal Motility

Two new techniques for studying gastrointestinal motility were described

Dr G Vantrappan and his colleagues (Chicago, Ill) have been able to obtain simultaneous fluorocinematography pictures and a record of intraluminal pressure on the same screen, and so to be certain of the type of peristaltic wave change inducing pressure changes This technique has been used to study normal deglutition, tertiary œsophageal contractions, and diffuse spasm of the œsophagus

In the second new technique (Dr J T Farrar [New York]) intraluminal pressures are recorded by the use of an ingestible, pressure-sensitive radiotelemetering capsule, or " radio pill " The capsule, 3 cm long and 1 cm in diameter, contains a replaceable battery lasting twenty-four hours, a frequency-modulation transistor radio transmitter, and a pressure-sensitive diaphragm Pressure change transmits signals to a frequency-modulation receiver, displayed on an oscilloscope and recorded on paper It has been found possible to obtain records from stomach, small intestine, and right colon which correlate well in frequency and appearance with those recorded by other methods This technique has a particular place in the study of functional disorders of small and large bowel over long periods

Dr Charles Code (Rochester, Minn.) spoke of the enormous potentialities of both methods

Carcinoidosis

In the Association's annual memorial lecture, Prof Jan Waldenström (Malmo, Sweden) discussed 156 cases of carcinoidosis He stressed the predilection of the endocardial lesions for the right side of the heart, the frequencies of valvular involvement being pulmonary 35, tricuspid 36, mitral 12, and aortic 4 He also produced histological evidence that the endocardial lesion is biochemically induced He described a case of carcinoidosis in which the primary tumour existed in a teratoma In some instances a severe pellagra-like syndrome is associated with the clinical picture, and Professor Waldenström suggested a possible biochemical reason for this association The antiserotonin drugs have proved disappointing, and no medical treatment is of value, surgical excision offers the only hope of remission

Effects of Serotonin on Gastrointestinal Tract

Dr B J Haverback (Los Angeles, California) said that serotonin and its precursor 5-hydroxytryptophan powerfully stimulate intestinal motility—an effect which is potentiated by lysergic acid diethylamide and inhibited by bromlysergic acid diethylamide and histamine-releasing substances Normal ranges of blood-serotonin and urinary 5-hydroxyindoleacetic-acid levels are 0 15–0 5 µg per mg of platelet protein and 2–9 mg per 24 hr respectively Studies on patients who had undergone intestinal resection suggest that the gastrointestinal tract makes a major contribution to the blood level and urinary output of serotonin

In the ensuing discussion it was pointed out that the urinary excretion of 5-hydroxyindoleacetic acid is temporarily increased after eating bananas, which contain large amounts of serotonin, that it is increased in the patient with idiopathic steatorrhœa in relapse, which is thus distinguishable from other types of steatorrhœa in which the urinary levels are normal Remissions induced by the gluten-free diet are accompanied by a decrease in the urinary elimination of 5-hydroxyindoleacetic acid to normal levels Raised urinary levels have also been observed in some patients with schizophrenia

Diverticulosis

Dr R S **Boles** and Dr S M **Jordan** (Boston, Mass) described a study of 294 patients with diverticulosis who were followed for between ten and thirty-one years 25% later had diverticulitis, and 6% developed symptoms attributable to diverticulosis—namely, obstruction, bleeding, and fistula formation While obstruction seems to be statistically related to the number of attacks of inflammation, bleeding and perforation seem to be unrelated to the number of attacks Cancer developed in 5% of patients with uncomplicated diverticulosis, in 3 6% of those with diverticulosis associated with complications, and in 6 8% of those with diverticulitis, but the correlation was not clear, and cancer commonly developed in areas unaffected by disease

Antibiotics

In a critical bacteriological appraisal of antibiotics for colon surgery, Dr I **Cohn**, Jr (New Orleans, Louisiana), found most of the drugs usually recommended—particularly sulphonamides—unsatisfactory in the control of the intestinal flora

He recommended a combination of neomycin and achromycin, and has obtained good results by injecting the antibiotics down a fine plastic tube to the anastomosis site

Regional Enteritis

A panel consisting of Dr J A **Bargen** (Rochester, Minn), Mr B N **Brooke** (Birmingham, England), Dr R B **Cattell** (Boston, Mass), Dr J B **Kirsner** (Chicago, Ill), and Dr F E **Templeton** (Seattle, Washington), with Dr B B **Crohn** (New York) as chairman, discussed regional enteritis

The ætiology of the condition remains obscure Familial examples of the condition have been reported, but heredity plays only a minor role Mesenteric glandular enlargement seems to be secondary rather than primary It is largely a disease of young people, in a large series the average age was 27 3 (range 4–74), it runs a long course and often recurs after operation—in fact, in the Mayo Clinic series 135 out of 400 patients had had recurrences after two to six years, and these recurrences were commonest in young people The ten-year-survival rate was 81%

Radiographic identification of the disease is extremely difficult, but with care is possible in 50% of cases Serial thirty-minute films after oral administration of flocculating barium suspension was recommended, but terminal ileum can usually be better displayed by a barium enema The stenosing lesion is easily identified, but other forms are difficult to detect The deficiency pattern and cobblestone mucosal change, though often helpful, are nonspecific

Mr Brooke described the distribution of the initial lesions in 121 patients these were duodenal or jejunal 14, ileal 48, ileocæcal 40, colonic and ileal 12, and colonic alone 7, thus 62 had ileal lesion alone, and 59 combined involvement of small and large bowel

As to treatment it was generally agreed that medical treatment should be applied initially, and surgery reserved for the complications of obstruction and fistula formation Bed rest, high-protein high-calorie diet, hæmatinics, blood-transfusion, and electrolyte replacement were recommended Neomycin or achromycin often relieve fever and toxicity, steroid therapy sometimes induces dramatic remissions, and it has not, in the panel's experience, induced perforation Dr Bargen has had good results from X-ray therapy in two to three courses of 600r

The surgical members of the panel asserted that medical treatment has never effected a cure, but surgery was still to be used only for the complications of the disease—resection was preferred to a bypassing operation A recurrence-rate of 34% was to be expected, but two-thirds of the patients treated at the Lahey Clinic and the Mount Sinai Hospital have had successful results from surgery In acute regional enteritis simulating appendicitis, the appendix should not be removed, appendicectomy predisposes to fæcal fistula Recovery ensues in the majority of these acute cases, which do not necessarily progress to the chronic form Before attempting to deal with perianal disease, a common complication, it is necessary to correct the intestinal defect Associated liver disease and carcinoma were regarded by most members of the panel as exceedingly rare

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New Inventions

AN AUTOMATIC CAMERA FOR USE IN OPERATING-THEATRES AND WARDS

This automatic camera can provide a day-and-night colour-photographic service in operating-theatre and ward and requires no skilled assistants for its operation The camera unit is positioned by an unsterile assistant under the direction of the surgeon, who controls by a foot-switch both the camera shutter and the focusing torches, which work on the range-finding or " dam-buster " principle

Apparatus

The camera unit, made of 'Perspex', is airtight to enable it to be used during the administration of all types of anæsthetic,

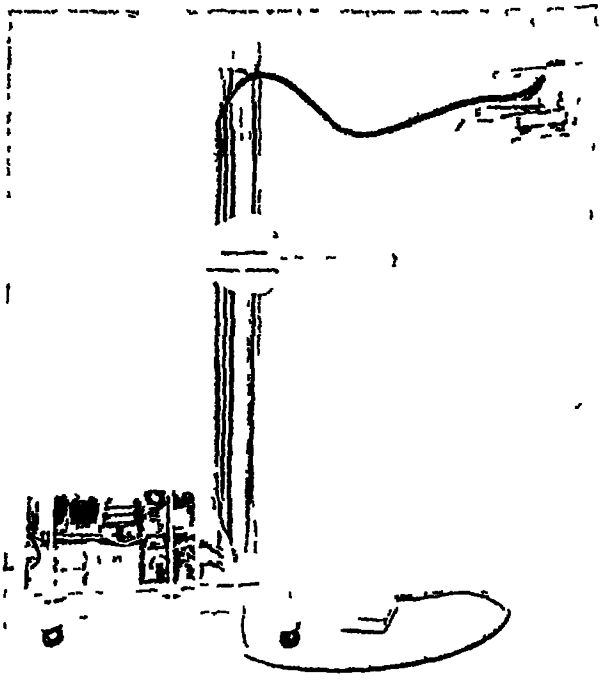

Fig 1—Automatic theatre camera

This is mounted on a stand similar to that used by mobile X-ray machines The camera unit is on an adjustable arm that can be swung over the operating-table The power pack on the base of the stand acts as a counterweight The foot-switch has two buttons, one switches on the focusing lights, the other operates the camera shutter it includes an electronic flash-tube and two pairs of focusing lights and is mounted on a stand similar to that used in mobile X-ray machines (fig 1) Mounted also in an airtight box on the stand is the power supply

The camera is a 'Robot' using 35 mm. film. In this camera film transport and shutter setting are done by clockwork, the foot-switch operates the shutter release through a solenoid (fig 2) Twenty-four exposures can be made before the camera clockwork has to be rewound.

The telephoto lens covers a field of $4^1/_2$ inches square at the near setting and 8 inches square at the distant setting Photographs are taken only in these two positions, the desired size of field being selected by manipulating a knob on top of the camera unit.

Each pair of torches is preset and fixed so that their light beams intersect, one pair at the near focus and the other at the distant focus of the camera lens, and illuminate the respective fields covered by the lens at each of these settings (fig 2) The wiring of the torches is arranged so that the appropriate pair is lit when the "focus" button on the foot-switch is depressed.

To take a photograph during an operation the camera unit is placed above the object, and the surgeon directs its raising or lowering until the focusing beams intersect on the object (fig 3), he can then take up to 24 photographs simply by pressing the "take" button on the foot-switch.

Illumination for the photograph is provided by a 310-joule electronic flash housed in an airtight reflector and arranged in a circle around the lens (fig 4) This arrangement gives intense illumination even in deep cavities and allows small lens-apertures to be used It thus gives a good depth of focus of about 4 inches on the small field and 6 inches on the large.

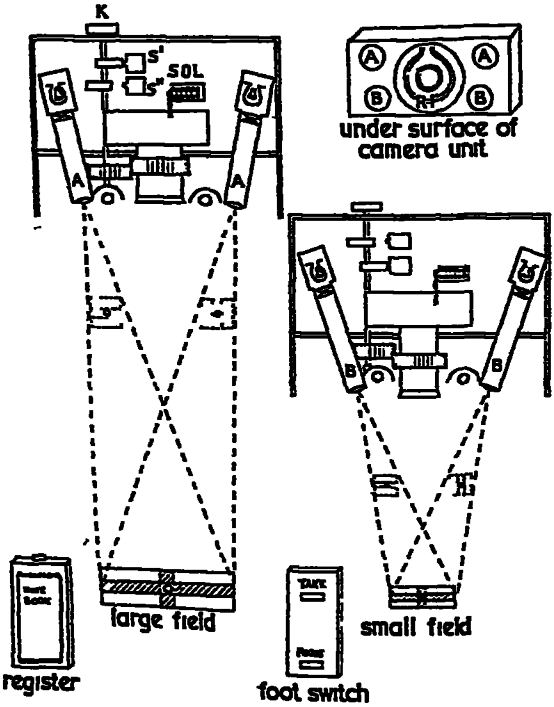

Fig 2—Construction of camera unit and focusing arrangement for two sizes of field A, torches for large field, B, torches for small field, operated by foot-switch 'focus" button, RF ring flash.

Knob K on top of camera unit adjusts lens focus, at each extreme of this movement switches S^1 and S^{11} operate so that appropriate pair of torches are lit when foot-switch button focus' is depressed When light beams intersect on object, surgeon depresses foot-switch button 'take", this energises solenoid (SOL) and operates camera shutter Clockwork mechanism in robot camera transports film and sets shutter for next exposure Up to 24 consecutive photographs can be taken in this way To ensure that subject matter of each photograph is recorded a switch is arranged so that apparatus will not work until lid of register has been raised.

An electrical device helps to ensure that details of each patient are entered in the record book kept under a hinged lid on top of the power pack, because when switched on at the mains the machine will not work until this lid has been raised

Results

Definition is of a high order because of the high optical quality of the lens, and because blurring from movement and vibration is eliminated by the extremely short duration of the flash —12 microseconds Colour values are constant, and it is not difficult to photograph such objects as the vagus isolated during an abdominal vagotomy

Advantages

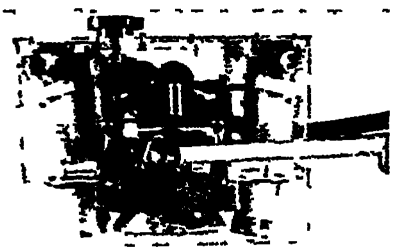

Fig 3—Torches act as rangefinders and enable camera unit to be placed at correct distance from object.

Each pair of torches is preset and arranged so that their beams intersect, one pair at near focus and other pair at distant focus of lens, and illuminate respective camera fields at each of these settings Torches are wired so that appropriate pair is lit when "Focus" button on foot-switch is depressed

Other arrangements for automatic photography in the operating-theatre have disadvantages with cameras in fixed positions, like that of the operating-lamp, it is difficult to arrange for more than one size of photographic field and, unless a flash unit is included, colour photography is impracticable, moreover, such a camera cannot easily be moved to another theatre, ward, or clinic and cannot even easily be used to photograph specimens removed at operation.

Photographic arrangements relying on a photographic technician are invariably subject to delay, and, unless a special gantry is available, it is often impossible for the photographer to reach the best vantage point above the sterile operation field.

The apparatus here described fulfils most of the desiderata and meets both clinical and medicolegal needs in all types of hospital

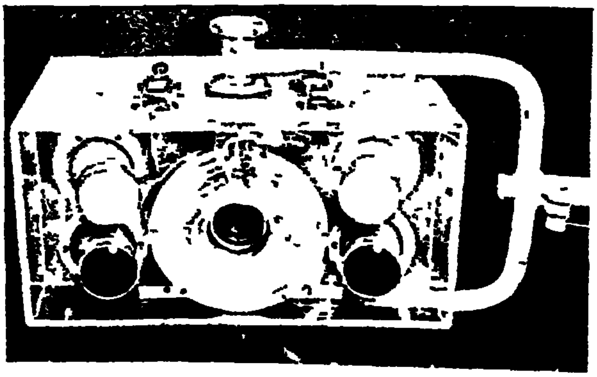

Fig 4—Undersurface of camera unit, showing two pairs of torches (one pair illuminated) and camera lens surrounded by reflector housing the ring-shaped electronic flash-tube

The prototype was built by kind permission of Dr R G Macfarlane, F R S, in the Nuffield hæmatology workshop, Radcliffe Infirmary, and the apparatus is now in commercial production I wish to thank Dr Macfarlane and Dr F Kemp for facilities, Mr E J Burrough and Prof T P Kilner for arranging financial assistance, and Mr A Lord for building most of the prototype

SPECIFICATION

Camera—Robot 2 A or ' Star ' Negative-size 24 mm x 24 mm on 35 mm colour film (' Kodachrome ') (30 exposures on normal 20 exposure length)

Lens—Schneider ' Tele-Xener ' 7 5 cm Iris diaphram aperture is adjusted automatically to f 14 for near focus and f 11 for distant focus

Flash—Ring-type 312-joule (fig 4)

Torches—Preset 48 watts each Contains lens systems and masks giving beams as shown in fig 2

Camera unit and power pack—Are mounted in airtight ' Perspex ' boxes

Focusing mechanism—By means of a gear the focusing-knob on top of the camera unit operates the focusing ring on the lens This is used only at each extreme of its focusing range In these positions the appropriate pair of torches is brought into circuit

Servicing—By releasing four clips the camera, together with the lens and electronic flash tube, can be easily removed from the rest of the camera unit for servicing

Radcliffe Infirmary,
Oxford

A M N GARDNER
B M Oxon, F R C S

Reviews of Books

Thinking

An Experimental and Social Study SIR FREDERIC BARTLETT, C B E, F R S, formerly professor of experimental psychology and director of the psychological laboratory, University of Cambridge London Allen & Unwin 1958 Pp 203 18*s*

So deeply dualistic are our basic assumptions about the nature of human behaviour that the suggestion that the skills of the mind have some features in common with the skills of the body may at first seem bizarre Sir Frederic, however, not only has been so open-minded as to invent such a hypothesis, but has been ingenious enough to test it The first chapters report the findings of his experiments on the formal processes of thinking, on interpolation and extrapolation, thinking stepwise and by intuitive jumps The significance of direction, sequence, and dependence on social background are illustrated Moving from the laboratory to the field and from " closed " to " adventurous " thinking, later chapters deal with thinking of the experimental scientist, of the artist, and of the man-in-the-street These activities are delineated with delightful originality and clarity so that many things we have vaguely or confusedly been aware of suddenly jump into focus

Thinking presents a distillate of years of reflection and investigation in a way which will interest both those pursuing research in the same field, and the rest of us who practise daily, willynilly and as best we may, the very kinds of behaviour described It is a quarter of a century since Sir Frederic's *Remembering* was published and many of its fruits are still ripening *Thinking* and also *The Mind at Work and Play* (which preceded it by seven years) will help to mature and extend the already abundant harvest Sir Frederic has made a splendidly growing and growth-promoting contribution to our understanding of human behaviour

A Centenary of International Ophthalmology (1857-1957)

SIR STEWART DUKE-ELDER, K C V O, F R C S London Henry Kimpton 1958 Pp 91 12*s* 6*d*

THE centenary meeting of the International Congress of Ophthalmology is being held this year in Brussels, where the first congress took place The ophthalmoscope had been demonstrated by Helmholtz in 1850 to the Physical Society in Berlin, and, by allowing the exploration of the inner eye for the first time, completely changed the scope and outlook of the specialty, a new science had been created, the implications of which were of immediate practical importance But in 1857 it was still not widely known and those who used it were being confronted almost daily by unsuspected clinical pictures which were new and difficult to interpret It seemed urgent, therefore, to extend the use of the instrument as widely as possible, and equally important that those who were already becoming familiar with it should meet together to collate their observations and agree on their meaning and significance It was therefore decided to hold an international congress

Sir Stewart's book tells something of the story of international ophthalmology in all its aspects, and it reflects exciting highlights in the advance of the subject The salient features of each meeting are briefly described, and most accounts are preceded by a small portrait of the president, including Fallot, von Graefe, Argyll Robertson, Snellen, and Sir Stewart himself The latter part of the volume deals with the work of the International Council of Ophthalmology, and ends with some wise remarks about the future of the Congress

Methods in Enzymology

Vol 4 Editors S P COLOWICK and N O KAPLAN London Academic Books 1957 Pp 914 £8 11s 6d

THE final instalment of this ambitious publication maintains the high standard of the preceding volumes The opening section gives an admirable survey of the principal methods used in the characterisation not only of enzymes but of proteins generally The first article is on electrophoresis and is by Arne Tiselius himself The middle section of the book, much the shortest, is a miscellany entitled Techniques for Metabolic Studies The articles by Britton Chance on spectroscopic observation of respiring cell-particles and that by O H Lowry on micromethods of enzyme assay are of outstanding interest In a contribution on histochemical methods it is disappointing to find not even the briefest general appraisal of this approach to cellular biochemistry On the other hand, the article by F S Sjöstrand on electron microscopy of cellular constituents (unexpected in such a context) is a very valuable review

The rest of the book is devoted to isotope techniques Here again the introductory articles (by D Sternberg and S Udenfriend on radioactive tracers and by A San Pietro on stable ones) are admirable The contributions which follow record radiochemical methods for the synthesis and degradation of compounds important in intermediary metabolism The article on the isolation of Krebs-cycle intermediates overlaps to some extent one dealing with the same substances (unlabelled) in the third volume, but the rarity of such overlap in a work of some 4000 pages is a tribute to the editors

Methods in Enzymology provides a valuable starting-point for anyone seeking information on practical problems in this and related fields of biochemistry, and it is also for many purposes a useful bench manual

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Medicine (7th ed London J & A Churchill *1958* Pp 847 45*s*)—The preface to the first edition *(1932)* of Dr G E Beaumont's textbook stated that it was meant as a short text for undergraduates and also as a help to general practitioners Psychological and dermatological medicine were purposely omitted, but otherwise it aimed to cover briefly the whole field of medicine, which it has successfully done for a long time Twenty-six years and six editions later, there has been a gigantic expansion of medical knowledge, not merely in the way of discoveries, about which the book is usually up to date and accurate, but in new ways of looking at old facts Inevitably, in the history of well-established textbooks, points are reached at which more radical revision or reconstruction is required, and perhaps, with the 8th edition ahead, this should now be considered

The Chemistry of Blood Coagulation (Springfield, *Ill* Charles C Thomas Oxford Blackwell Scientific Publications 1958 Pp 194 34*s*)—This is a translation by Dr Robert Hartmann of *Paul Morawitz*'s original work which set out the theories of blood coagulation from which our present-day ideas spring It has considerable *historic* interest and it is surprising to see that *Morawitz* was able to quote 490 references A glossary of terms used by Morawitz, with their equivalents in present nomenclature, is very helpful The translation is smooth and easy to follow

THE LANCET

LONDON 21 JUNE 1958

Agammaglobulinæmia

The discovery that extreme susceptibility to infection in some patients is related to very low levels of γ-globulin in their serum has opened a field of investigation which is being eagerly explored by physician and immunologist alike. γ-globulin may be separated into several subfractions by electrophoretic and immunological techniques. While one method may fail to reveal any at all, another may show some—presumably because they measure different subfractions Nevertheless, the term "agammaglobulinæmia" looks and sounds better than the more unwieldy "hypogammaglobulinæmia" It is already certain that there are various types of agammaglobulinæmia, and a satisfactory classification will depend on further elucidation of the physical, chemical, and immunological properties of the various subfractions Firkin and Blackburn[1] have suggested a working classification which will, no doubt, require subsequent modification.

Congenital agammaglobulinæmia was first described by Bruton[2] in a boy with recurrent bacterial infections Over 50 cases have now been reported in patients of European extraction[3-9], this disorder has not so far been recorded in Southern Europe or Latin America Nearly all the cases are in males, which suggests inheritance as a sex-linked recessive characteristic. This would not exclude an occasional case in females, but the case in a girl reported by Pearce and Perinpanayagam[10] was almost certainly of a different type because splenomegaly and lymphadenopathy, noted in their patient, have not been reported in boys Agammaglobulinæmia should be suspected when a young child has repeated bacterial infections in the absence of any other discoverable cause. The γ-globulin level of the serum in such cases varies from 0 to 25 mg per 100 ml with different methods of analysis These children have all shown an apparently normal clinical response to virus infections and to vaccination against smallpox, but virus antibodies are not found in their serum after immunisation against smallpox, poliomyelitis, or other virus antigens or after the virus infections themselves[6] Bacterial antibodies are not formed on stimulation with bacterial antigens such as T.A.B vaccine, and the Schick test remains positive after injections of diphtheria prophylactics. Isohæmagglutinins are absent or are present only in extremely low titres Plasma cells are very scanty in lymph-nodes, bone-marrow, or the inflammatory lesions themselves, this conforms with the view that these cells are the chief source of γ-globulin[11] The role of the lymphocyte is less certain, much reduction in lymphoid tissue seems to be a constant finding, but lymphopenia has not always been observed Neutropenia and eosinopenia are common[6] Good[12] reported successful skin homografts to 2 patients with congenital agammaglobulinæmia, and long survival of a skin transplant in a hypogammaglobulinæmic adult. Normally this is only possible between identical twins, because in other individuals antibody-production kills the transplants Transplants of skin from agammaglobulinæmic patients to normal persons fail, the rejection being associated with plasmocytosis in the skin and regional lymph-nodes The recurring bacterial infections in these young children usually yield rapidly to antibiotics, and they may be prevented by regular injections of γ-globulin[3] with or without protracted antibiotic prophylaxis

Primary acquired agammaglobulinæmia may be diagnosed in patients of either sex in whom recurrent bacterial infections start after early childhood, and in whom the γ-globulin level of the serum is below 100 mg per 100 ml. without other discoverable cause. The deficiency of γ-globulin tends to be less complete than in the congenital disease, immunoglobulins and isohæmagglutinins tend to be formed rather better, and there may be bacterial antibody formation to some antigens but not to most. Enlargement of the spleen and lymph-nodes is common[13-15] Several patients have been shown to have steatorrhœa, and others have presented with bronchiectasis[5 16-17] Leucopenia is common and has in some cases been relieved by splenectomy[5 14] Deficiency of plasma cells is a notable feature, as in the congenital cases[5 14] Firkin and Blackburn[1] have suggested that the acquired condition may be classified into three subgroups according to whether the lymph-nodes show (1) absence of germinal centres, (2) "benign" follicular hyperplasia, or (3) replacement of normal architecture by granulomatous tissue In fact, they have suggested that the disease may represent a mild form of reticulosis, which would make their division of acquired agammaglobulinæmia into primary and secondary forms somewhat unreal On the other hand, Citron[14] found hypergammaglobulinæmia in relatives of each sex of his 2 patients Young et al[18] recorded the same finding in the healthy mother and brother of a man with agammaglobulinæmia. This suggests that genetic factors may play a part even in the acquired form of agammaglobulinæmia

The behaviour of tuberculous infections in both the congenital and the acquired forms of primary agammaglobulinæmia contrasts strikingly with that of other bacterial infections Clinically, the acquired immune response to tuberculous infection seems to function normally in the absence of γ-globulin.[19] It might have been expected that such patients would not show delayed tuberculin hypersensitivity But one of the agammaglobulinæmic brothers described by Elphinstone et al [8] had primary intrathoracic tuberculosis with a positive Mantoux test, his disease ran a normal course, recovery being hastened by chemotherapy, his sibling reacted normally to B C G, with subsequent Mantoux conversion Parkes [19] has described the case of a woman with acquired agammaglobulinæmia who had sputum-positive pulmonary tuberculosis and a positive Mantoux test, her clinical course seemed to be no different from that of others, but she had repeated severe pyogenic infections Furthermore, delayed hypersensitivity to tuberculin has been produced in a hypogammaglobulinæmic patient by subcutaneous homograft of lymph-node from a sensitised donor [20] Immunologically tuberculosis behaves quite differently from other bacterial infections

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[16] Sanford J P, Favour, C. B., Tribeman, M. S *New Engl J Med.* 1954 250 1027
[17] Cooke, W T, Weiner, W, Shinton, N. K. *Brit med J* 1957, i 1151
[18] Young, I I Wolfson, W Q, Cohn C. *Amer J Med.* 1955, 19, 222.
[19] Parkes, R. *Brit med. J* April 26, 1958, p 973

In contrast, there is evidence that agammaglobulinæmic patients may be highly susceptible to protozoan infections In 1955 Hutchison [7] reported the first case of congenital agammaglobulinæmia in this country The pneumonia which caused the death of this patient, a boy aged 1 year and 8 months, comprised bilateral massive consolidation with a peculiar intra-alveolar acellular exudate and greatly thickened alveolar walls due to infiltration of round cells, a few polymorphs, and some macrophages, no plasma cells were recognised in the interstitial infiltrate Five years previously this child's brother had died at the age of 6 months of an identical type of pneumonia, and it seemed probable that he had had unrecognised agammaglobulinæmia Hutchison [21] subsequently reported that H S Baar had pointed out to him that the cause of the pneumonia in both siblings was infection with *Pneomocystis carinii* This protozoan infection is commonly described, under the name "interstitial plasma-cell pneumonia", in young infants in Central Europe, but it has only very rarely been described in this country No doubt the absence of plasma cells in Hutchison's cases was due to the agammaglobulinæmia Last year Bird and Thomson [9] described 2 further fatal cases of *Pneumocystis carinii* pneumonia in male infants, 1 of whom had been shown to be agammaglobulinæmic The lung sections in these cases showed appearances identical with those found in Hutchison's cases, including absence of plasma cells, and probably both infants had congenital agammaglobulinæmia *Pneumocystis carinii* infection does not respond to antibiotics Its presence should be suspected in any infant or child with an antibiotic-resistant pneumonia, and the level of the γ-globulin in his serum should be estimated

Secondary acquired agammaglobulinæmia has been described in various disorders of the reticulo-endothelial system such as myelomatosis, lymphoma, and chronic lymphatic leukæmia [1] Some but not all of these patients are unduly susceptible to bacterial infections

Transient hypogammaglobulinæmia of infancy is physiological, in that the level drops in the 1st month of life to a third of the value at birth It starts to rise again about the 3rd month, but the adult value is not reached until the age of 2 years [22] Good [12] has studied a woman with acquired agammaglobulinæmia during pregnancy In the first trimester she failed to respond to antigenic stimulation, but a significant response occurred during the last thirty days After delivery of the fœtus and placenta the immune response in the mother was no longer demonstrable The child was agammaglobulinæmic in the first 2 months of life During the 3rd month the infant began to produce γ-globulin, to make antibody, and to show plasma cells in the reticulo-endothelial tissues In some instances the low level of γ-globulin may persist longer and be associated with infections 4 fatal cases which were probably in this category were associated, not with bacterial or protozoan infections, but with vaccinia gangrenosa [23-25] The pathological findings have also differed from those in congenital agammaglobulinæmia in that although, as in the latter, lymphoid tissue is diminished with a notable reduction in germinal centres, plasma cells and monocytes may be numerous Furthermore, 1 of these patients was a female infant [23] It seems that some of the very young infants with "interstitial plasma-cell pneumonia" ascribed to *Pneumocystis carinii* in Continental reports may have had this type of hypogammaglobulinæmia

Firkin and Blackburn [1] include two other much less clearly defined categories in their classification Hypogammaglobulinæmia associated with hypoproteinæmia is most often seen in the nephrotic syndrome, but there remains an ill-defined group of patients with hypoproteinæmia and low γ-globulin level who present with episodic œdema but rarely with infections Hypogammaglobulinæmia with the familial dysproteinæmia of Homburger is characterised by familial œdema of the legs, ulcers of the legs in males, and functional vascular changes in females Dysproteinæmia may be detected only by electrophoresis and may vary from one relative to another

Local-authority Dental Services

The reports of medical officers of health and school medical officers are beginning to make their annual appearance, and almost without exception they draw attention to serious understaffing of the dental services Over the country as a whole, there are now no more local-authority dentists than there were before the war, prospects for development are definitely not bright, and there seems to be little hope of the present maternity and child-welfare and school dental services evolving to become a nation-wide comprehensive service It would be incorrect, however, to conclude that all parts of the country are suffering equally, or even to assume that, because the local-authority service in one locality happens to be well staffed, the priority classes there are necessarily much better provided with dental

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20 Martin C M, Waite, J B, McCullough, N B *J clin Invest* 1957, 36 405
21 Hutchison, J H *Lancet*, 1955, ii, 1196
22 Orlandini, O, Sass-Kortsak, A, Ebbs, J H *Pediatrics*, 1955, 16, 575
23 Keidan, S E, McCarthy, K, Haworth, J C *Arch Dis Childh* 1953, 28, 110
24 Kozinn, P J, Sigel, M M, Gorrie, R *Pediatrics*, 1955, 16, 600
25 Somers, K *Arch Dis Childh* 1957, 32, 220

care than in areas where shortage of staff exists The quality and quantity of dental attention that the children and expectant and nursing mothers of a given area receive is nowadays increasingly a function not only of the number of full-time dentists employed by the local authority but also of the number of dentists in the National Health Service who regularly treat children and the proportion of their time they are willing to reserve for the priority groups In areas where there are few local-authority dentists but relatively many private practitioners treating the priority classes, it is possible for the latter group to compensate for the deficiency in the former

The wide discrepancies in resources between one area and another cannot be justified, and a survey of the overall position seems to be the essential next step By correlating the number of local-authority dentists in each area, the number of private dentists regularly treating the priority classes under the National Health Service, and the proportion of their time devoted to this work with the size of the local population, it should be possible to identify the “ black areas ” in which facilities are inadequate Such an inquiry could be carried out for the Ministries of Education and Health, which could then try, in cooperation with the local authorities concerned, to redress the balance by stimulating recruitment of local-authority dentists into these areas, perhaps by the offer of houses and perhaps also by “ weighting ” the national salary-scale in favour of otherwise unattractive parts of the country Such a policy would probably entail the abandonment, for the time being, of national recruitment and competition between the local authorities for the services of the relatively few dentists attracted to salaried posts, in favour of an attempt to persuade those members of the profession willing to enter or already in the local-authority service to move to areas where the need for their services is greatest If successful, this measure would at least result in a more equitable distribution of limited numbers Its effects could be enhanced if, in addition, National Health Service dentists could be persuaded to devote more of their time to young children, perhaps by payment of a special bonus to practitioners in the “ black areas ” who were willing to give regular comprehensive treatment to a certain number of children each year

It seems quite unrealistic to hope to build up a comprehensive service for the priority groups on the basis of the few dentists at present attracted to appointments under the local authorities, and the most urgent problem is to ensure that those who do take such appointments go to areas where they are most needed

Annotations

INTERNIST INTO INTERNATIONALIST

LAST week in London Prof Howard Rusk of New York described how the war changed some of his ideas on what matters most in medicine He was giving the third Horder lecture, founded by the British Spas Federation, and Prof R E Tunbridge, chairman of the Federation, presided over an audience which included the Minister of Health

Before 1942 Dr Rusk was an internist in Missouri, and he came of the school of thought which sets most store by the intricacies of diagnosis Having hitherto regarded convalescence as something hardly worth bothering about, he suddenly found himself organising an Air Force rehabilitation centre He was impressed first by the appalling amount of time wasted in hospital by Service patients who ought to have been actively prepared for the quickest possible return to military duty In attempts to remedy this, various trials proved the advantages of early ambulation This was not a new discovery, for it had been recommended by a gynæcologist to his scornful colleagues of the New York Academy of Medicine in 1905 Nearly forty years after this pioneer was suppressed by the critics, “ we began to learn ”, Dr Rusk said, “ that rest in bed ought not to be used indiscriminately and could be dangerous” Merely going to bed, it was found, produced negative nitrogen and calcium balances and reduced cardiovascular efficiency

From this work his attention turned to the restoration of the men with permanent disabilities At the end of the first world war, less than 10% of the U S 400 paralysed soldiers and sailors survived to need rehabilitation, but after the second war there were 2500 of them—strong young men, with good heads and hands, who wanted to do the best they could with the rest of their lives Thanks to an active programme, parallel to the British one centred on Stoke Mandeville, 1763 of these men are now living at home and driving their own cars, and 1400 are doing some kind of work

But if this could be done for Servicemen, why should it not be done for the civilian, of whom there were some 12,500 paralysed during the same period? Why should a distinction be made between the wounded in war and the wounded at home—disabled in industry or automobile accidents? In the ten days after D-day in Normandy, the American Forces had 11,000 killed and wounded, but in the same ten days no fewer than 26,000 were killed and wounded on the highways and in the factories of their own country To give the same chances to the civilian disabled as to the soldiers, much leeway had to be made up and much work was needed of hemiplegics alone, the number in the U S A is put at 1,400,000 But what can be done by active treatment is shown by the fact that of 3000 hemiplegics (of average age 63) 88% were able, within nine months, to cope with the needs of daily life at home, and 40% were in gainful work For patients to do well, Dr Rusk found they needed three things—someone to love them, a home to go to, and a job to go to

Lord Horder, he said, was one of the first to become interested in this new yet old specialty of rehabilitation, and in his original address to the Chartered Society of Physiotherapists he had put the emphasis not on passive methods of treatment but on getting patients to do things for themselves He used stress as a therapeutic friend, and Dr Rusk, too, holds that stress, in the sense of something that forces activity, is necessary for recovery and for a happy life If the stresses of work are suddenly removed on retirement at 65, the result may be disastrous, so old people should continue to have jobs of one kind or another, though not necessarily their old ones They need above all an object, and he had seen astonishing results in a club formed for over-65s—people without anywhere to go This club has committees for everything (one committee to serve the tea and another to serve the coffee), there are bridge-drives and dances and weddings, and, while the hospital admissions of these old people for physical illness have fallen by half, their admission for senile psychosis has actually ceased This, said Dr Rusk, is real preventive medicine—the preventive medicine of the future Though he admitted that it was unscientific to say so, he believes that a purpose in life, and being happy, does something to prevent the progression of arteriosclerosis

Having just returned from an international conference called by the International Labour Office to discuss rehabilitation of the disabled workers, Dr Rusk ended his lecture by endorsing the plea of a Russian representative that against disability we should all work together He has never, he said, been anywhere in the world where doctors—regardless of race, creed, colour, politics, and curtains—do not have a common language and a common purpose In the healing arts we have a tremendous responsibility and also a tremendous opportunity In this world that is so technologically precocious and spiritually adolescent we can, if we try, build at least one block of international understanding

SMOKING AND PAPILLOMA OF THE URINARY BLADDER

IN Denmark Clemmesen et al [1] investigated the smoking habits of patients with papilloma of the urinary bladder, and they conclude that among men with this disease there is a lower proportion of non-smokers than there is among the healthy, and that, where patients smoke only *one* type of tobacco preparation, cigarettes, cigars, and cigarillos are implicated, but not pipe-smoking They noted that admission to hospitals in Copenhagen of patients with papilloma of the bladder had increased steadily from the three-year period 1944–46 up till the period 1953–55 The numbers were respectively 22 and 110 in men and 4 and 40 in women From information previously gained from the Danish Cancer Register it is stated that the increase in incidence of bladder tumours, both benign and malignant, has occurred in men but not in women and follows closely that of bronchial cancer—though this is not borne out by the hospital figures cited in their report Clemmesen et al questioned patients still alive between March, 1956, and November, 1957, about their smoking habits and compared the information thus gained with similar information from healthy persons obtained for another purpose in 1952–53 But 153 patients (more than a third) were not interviewed on account of lack of response (31) or death or inability to trace their whereabouts (122)

Lilienfeld et al [2] suggested provisionally, from a retrospective survey of clinical records of patients admitted to hospital with urinary-bladder cancer, that a significantly larger proportion of the men had smoked cigarettes for longer than had other classes of patients chosen for comparison, no such association was found in women Holsti and Ermala [3] swabbed the lips and oral cavities of mice with tobacco tar for 140 days and reported that they had observed both benign and malignant papillomatosis of the bladder at the end of a year of observation But no confirmation of this finding has been described

An association between papilloma and cancer of the bladder on the one hand and the manufacture, purification, and usage of certain aromatic amines on the other is well established in every country where such an industry exists In the future it should be possible to predict with some degree of certainty that certain chemicals are likely to be carcinogenic, but it will be far more difficult to tell which will be non-carcinogenic The risk is not confined to the aromatic intermediates from which dyes are made the finished dyes may also be carcinogenic, especially the azo compounds, and some of these, or their close chemical relatives, are in use as food dyes in some countries The exogenous causes of bladder papilloma and cancer is receiving concentrated investigation, and in this chemical age it is to be expected that the incidence will rise for reasons unconnected with tobacco smoking

THE CURE OF SOULS AND BODIES

FROM earliest times the Churches have shared with doctors the responsibility for the care of the sick, and the origins of many of our oldest hospitals show the value and strength of this ancient alliance But with the growth of scientific medicine, the partnership became uneasy The doctor was less ready to share with the priest the responsibility for his patients Today he is becoming increasingly aware of the effect of the patient on the disease and of the need to treat the person rather than the case This shift of emphasis has led many doctors to reconsider their attitude The Church of England [1] and the Church of Scotland [2] have also been considering their duties and responsibilities towards the sick in the modern world, and in the reports which Commissions of both churches have lately presented the thoughtful doctor will perhaps find a form of contract for a new and firmer partnership

Both Commissions are reserved in their attitude towards medically inexplicable healings Though they do not deny that these may occur they recognise that so-called miracles may be acclaimed in good faith by the layman who, unlike the doctor, is unaware of the normal course of a disease and possible natural remissions The Anglican Commission, which acknowledge the help they received from a committee of the British Medical Association,[3] wisely point out that many people are too ready to admire the unusual, and too slow to recognise the wonder of the familiar They regret " the popular idea that what can be scientifically explained has little or nothing to do with God " The Scottish Commission insist that " problems affecting physical and mental health require consideration *first* by a physician " and that spiritual healing should only be used with great discretion and always in consultation with the patient's doctor

The Anglican Commission suggest that the rigid separation of the spiritual and physical " which has, without doubt, enabled medicine (as much as other sciences) to make progress " has now outlived its usefulness, and both Commissions believe that the patient would now gain by closer cooperation between the churches and the doctors Doctor and priest, the Anglican Commission hold, need to respect each other's skill and understand the purpose of each other's work, and this will not be achieved by

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[1] Clemmesen, J , Lockwood, K , Nielsen, A *Danish med Bull* 1958, 5 121

[2] Lilienfeld, A , Levin M , Moore G *Arch intern med* 1956, 88, 129

[3] Holsti, L , Ermala, P *Cancer*, 1955, 8, 679

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[1] The Church s *Ministry of Healing* 1958 *Pp 84 2s 6d* Obtainable from the Church Information Board, Church House, Westminster, S W 1 *The medical members of the Archbishops Commission were* Mr B S Brentnall, *Dr Denis Brinton*, Dr Ronald Cove-Smith, Dr J A Hadfield, Dr R A Henson, Lady Jefferson, Prof Alan Moncrieff, Sir James Paterson Ross, Dr Joy Patrick, and *Dr David* Stafford-Clark

[2] *Report of the Commission on Spiritual Healing 1958* Obtainable from the Publications Department, Church of Scotland *121, George* Street, Edinburgh, 2 The medical members of the Church *of Scotland s* Commission were Dr W A Alexander, Prof Stanley Alstead, Sir *David Henderson*, Dr G W Ireland, Dr *Marjorie* Keith, and Mr G H Stevenson

[3] Divine Healing and Cooperation between Doctors and Clergy London, 1956

keeping out of each other's way Consultation over individual patients is the easiest and most natural way to draw priest and doctor together, but both Commissions suggest that this could be extended by meetings between small groups of clergy and doctors to exchange views and experiences They also propose that medical and theological students should be given an opportunity of learning something of the work and responsibilities of each other's profession The Scottish Commission was able to report that in at least one of their theological colleges a course of lectures is given to final-year students by the medical superintendent of a mental hospital and that the students visit the wards of the hospital Another opportunity for cooperation which the Scottish Commission urge is in hospitals with chaplains They would like to see the chaplain treated as a recognised member of the staff and drawn more often into consultation with his medical colleagues

In their training and approach the doctor and the priest inevitably differ But they share a common concern for the patient, and when a patient seeks help from both it will be most effectively given by colleagues who respect and trust each other

ANTICHOLINESTERASE INHIBITORS

THE anticholinesterases commonly used in the diagnosis and treatment of myasthenia gravis are neostigmine, pyridostigmine, and edrophonium Less commonly used are organophosphorous compounds with powerful anticholinesterase activity—di-isopropyl fluorophosphate and tetraethyl pyrophosphate Overdosage of an anticholinesterase may lead to a " cholinergic crisis " due to accumulation of acetylcholine in the tissues This stage is often difficult to recognise Clinical deterioration after an intravenous dose of edrophonium is evidence of the cholinergic state, and, because of the drug's transient action, this test is fairly safe Until recently there was no specific therapy for anticholinesterase poisoning The main weapons were withdrawal of neostigmine and administration of atropine, which neutralises the gastrointestinal, bronchial, and cardiac effects A free airway must be maintained, and sometimes mechanical aids to respiration are necessary *d*-Tubocurarine has been recommended[1], but the dose needed for " competitive blocking " of anticholinesterase is uncomfortably close to that producing muscular paralysis The action in man of two specific anticholinesterase inhibitors has now been thoroughly studied by Grob and Johns[2]

These substances are pyridine-2-aldoxime (2-P.A M) and diacetyl monoxime (D.A M) They were found to reverse cholinesterase inhibition and neuromuscular block due to organophosphorous or quaternary ammonium anticholinesterases 2-P A M proved the better of the two when administered before or after other anticholinesterases A very large dose of 2-P A M can produce a neuromuscular block in animals, but in man the recommended dose—1–2 g intravenously—is unlikely to have this effect Clearly 2-P A M should now be held ready for emergency therapy in cholinergic crises Unfortunately at this serious stage many myasthenics are in a precarious balance between the progressive disease and high neostigmine dosage, thus, whatever treatment is applied, many may fail to recover Namba and Hiraki[3] found that these two substances also counteracted ' Parathion ', an organophosphorous insecticide which sometimes gives rise to accidental poisoning

A NEW HOSPITAL REGION

THE South West Metropolitan Regional Hospital Board, responsible for a vast straggling area and a population of nearly 5 million, has deliberately fostered partial autonomy in its most distant sector—that of Wessex (Hampshire, Dorset, Wiltshire, and the Isle of Wight) The Minister of Health has now announced that the autonomy is to be complete from April 1 next year, when a Wessex Regional Hospital Board will come into operation The new region, which is compact, contains about 1³/₄ million people, and in it every specialty except neurosurgery is already covered If Southampton were eventually to have a medical school, this might end the region's reliance on London, but meanwhile it is likely to continue its association with the University of London—notably the British Postgraduate Medical Federation and the three undergraduate teaching hospitals (St George's, St Thomas's, and Westminster) that are linked with the South West Metropolitan region

Ten years ago a Wessex hospital region would have had to rely on London for many specialties Today that is no longer so The fact that the new region will from the start be so largely self-reliant testifies to the remarkable improvement, during the past decade, in hospital services outside the capital

ANTIBODY FORMATION IN VITRO

THE mechanism by which antibodies are formed is not completely understood, but it has been found that lymph-nodes transplanted from an immunised animal to a normal animal continue to produce antibody in the new host Washed cells from the lymph-nodes of an immunised rabbit give rise to antibodies when injected intravenously into a normal rabbit[1] Antibody formation also occurs in vitro in cultures of various tissues removed from immunised animals[2,3] Some interesting experiments which carry the matter a stage further are now reported[4] by Dr Nossal and Professor Lederberg, well known for his work on bacterial genetics in the University of Wisconsin, who has been the Fulbright visiting professor in Melbourne

Rats were each immunised with two different strains of salmonella and the popliteal lymph-nodes were excised Cell suspensions were prepared from these lymph-nodes, and by micromanipulation methods single cells were isolated Some of these single cells when incubated in a serum-saline medium produced antiflagellar antibodies capable of immobilising one or other of the bacterial strains with which the rats had been immunised

Quite apart from the interesting possibility of demonstrating antibody formation in vitro by single cells, this achievement makes it possible to investigate various problems of antibody formation The two salmonella strains used had different specific flagellar antigens, and the rats produced two distinct antibodies each capable of immobilising the specific strain The question arises therefore whether the two kinds of antibody are produced by a single cell or whether a separate cell is necessary to produce each kind of antibody In the experiments reported, 456 single cells were tested for antibody production, and of these 33 were active against *Salmonella adelaide* and 29 against *Salmonella typhi*, but none of these 62 immobilised both strains Possibly some cells may have

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[1] Churchill Davidson H C, Richardson A T *Lancet* 1957, i, 1221
[2] Grob D Johns R J *Amer J Med* 1958, 24 497, 512.
[3] Namba, T Hiraki, K *J Amer med Ass* 1958 166, 1834.

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[1] Harris S, Harris, T N Farber, M B *J Immunol* 1954, 72, 148
[2] Fagreus, A *ibid* 1948, 58, 1
[3] Keuning F J, van der Slikke L B *J Lab clin Med* 1950, 36, 167
[4] Nossal, G J V, Lederberg, J *Nature, Lond* 1958, 181, 1419

produced a very small amount of the second antibody in addition to the predominantly large amount of the main antibody, but the conclusion seems valid that "when an animal is stimulated with two contrasting antigens, individual cells tend to form one species of antibody" There remains the problem of why this is so Is it an interference phenomenon, and can a cell deal with only a single antigen at a time? Or is a cell genetically restricted to the kind of antigen to which it can form antibodies? In order to answer such questions it may be necessary to go back to a previous stage in the process—that of the initial stimulus to antibody formation

ARTIFICIAL RESPIRATION

It has been proposed that an old method for artificial respiration, and a variant of it, should be used for emergency resuscitation Safar et al [1] maintain that, used properly, mouth-to-mouth insufflation is far better than any of the push-pull methods certainly the figures given for the ventilation achieved suggest that their technique is efficient They criticise the method originally used for testing and comparing the different manual methods of artificial respiration They point out that in all instances the patients, though anæsthetised and curarised, were also intubated, thus ensuring a clear airway When they tested methods such as the arm-lift/back pressure (Holger-Nielsen) on patients who were not intubated the volume per respiration was low—not much above that which would wash out the dead space Without intubation, and even in the prone position, the toneless soft palate and pharynx partly block the airway and severely limit possible ventilation Even with intubation Safar et al did not succeed in moving more than 700–260 c cm of air with either the Holger-Nielsen or the Silvester method This is far below the ventilation regularly attained in the investigation of Gordon et al,[2] but the reason for this difference is not clear

Safar et al tested the mouth-to-mouth method with the subject on a hard table and on the floor They point out that one advantage of the method is that the operator has both hands free to hold the lower jaw forward and to keep the mouth open, thus ensuring a clear airway, at the same time the hands can be used to close the patient's nostrils The operator places his own mouth well over that of the patient and, at first vigorously, and later less vigorously, blows out his own expired air until the patient's chest expands The operator then removes his mouth and allows expiration to occur naturally by elastic recoil It is claimed that this method can be used by anyone on anyone, that it can be maintained for long periods without fatigue or dizziness, that it easily achieves a ventilation of 1000–1500 c cm at 12–20 respirations a minute, and finally that it is easily taught and learnt Occasionally air may enter the patient's stomach, but it can be removed by compression of the abdomen, and it does not interfere with the respiratory process The main objection to the mouth-to-mouth method is æsthetic, and to overcome this Safar et al have designed a simple S-shaped tube which can rapidly be inserted down to the pharynx, the operator can then expire through the outer end of this tube, giving oropharyngeal respiration The ventilation by using the tube is just as good as in the direct mouth-to-mouth method Insertion of the tube is said to be easy, to be soon learnt, and to involve negligible delay in starting resuscitation Further, the tube is small and light and can easily be carried in the pocket Mouth-to-mouth resuscitation can be used on patients of all ages, but Safar et al emphasise that for infants the operator must not expire vigorously lest he rupture alveoli, little more than an expiratory puff is required

Safar et al state that they tried the Holger-Nielsen method after inserting their pharyngeal tube and found that ventilation was extremely poor unless the lower jaw was held forward—obviously an impossible manœuvre for a rescuer working single-handed It is difficult to reconcile this and some other criticisms of the Holger-Nielsen and Silvester methods with the successes known to have followed their use,[3] and even that of the far less efficient Schäfer method It is also difficult to see how dizziness is avoided if the operator is hyperventilating sufficiently to supply "virtually room air" to the patient If the operator does not hyperventilate the method is open to objection by those who believe that 4–5% CO_2 should not be supplied to one who is anoxic and probably hypercapnic Nevertheless, though most people cannot be expected always to carry an oropharyngeal tube and must therefore stick to the Silvester or Holger-Nielsen methods, all workers who are likely to be faced by emergencies might well learn and test this simple method, and, if they find it good, use it All the speakers in an American Symposium on this method[4] spoke favourably of it Certainly no unreasonable conservatism should be allowed to prevent progress in saving life or preventing that death in life—the decerebrate state resulting from anoxia

BIRTHDAY HONOURS

The award of the Order of Merit to Sir Macfarlane Burnet, the distinguished virologist and immunologist, will be widely and warmly welcomed Burnet graduated in medicine in the University of Melbourne, where he is now director of the Walter and Eliza Hall Institute of Medical Research, and he devoted two periods to study and research in this country, in 1926–27 at the Lister Institute and in 1932–33 at the National Institute for Medical Research at Hampstead But he has spent most of his life, in biological and medical research of one kind or another, in Melbourne, where he has built a school which attracts workers from all over the world He has done much fundamental work on bacteriophages, and recently he has made equally detailed researches into the influenza viruses, and their methods of penetrating cells and multiplying therein In these two fields he has profoundly influenced scientific thought He is probably better known, however, for his ability to generalise in matters of wide biological significance

Doctors in the Dominions figure prominently elsewhere in the Honours List Thus Dr C R Burns and Prof F H Smirk, of New Zealand, are appointed K B E, and Prof J C Eccles, Mr B T Edye, and Brigadier K B Fraser, of Australia, and Colonel A G Curphey, of Jamaica, are created knights Of the honours to doctors in this country, the appointment of Mr J D McLaggan as K C V O and the knighthood conferred on Brigadier J S K Boyd and Mr E W Riches will give special pleasure to many We congratulate these and the others named in the list on p 1332

Sir Arnold Stott, consulting physician to the Westminster Hospital, died at his home in Surrey on June 15 at the age of 72

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[1] Safar, P, Lourdes, A E, Elam, J O *New Engl J Med* 1958, 258, 671

[2] Gordon, A S, Raymon, F, Sadove, M, Ivy, A C *J Amer med Ass* 1950, 144, 1447

[3] See *Lancet*, 1952, i, 548

[4] *J Amer med Ass* 1958, 167, 317–341

Public Health

OUTBREAK OF POLIOMYELITIS IN A SMALL URBAN COMMUNITY

R D PEARCE
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MEDICAL OFFICER OF HEALTH TO THE URBAN DISTRICTS OF BRIGHTLINGSEA, CLACTON, AND FRINTON AND WALTON, AND THE RURAL DISTRICT OF TENDRING, ASSISTANT COUNTY MEDICAL OFFICER

POLIOMYELITIS broke out in Brightlingsea (population about 4500) in the spring of 1957, 46 cases being notified in seventeen weeks, and 40 of these being subsequently confirmed clinically (table I)

Brightlingsea, an east-coast yachting centre, is situated on the eastern side of the Colne estuary in East Essex The two main industries are the building of small ships and boats and the oyster fisheries

Originally the town was probably an island Today it is served by one road three miles long, which connects Brightlingsea with the Colchester–Clacton Road, B1027 A single railway line connects the town with the main Clacton line The surrounding countryside is agricultural, and therefore a small urban community exists Most of the inhabitants work in the town, but an increasing number work in a large town about nine miles distant The accompanying map shows the relations of Brightlingsea

TABLE I—AGE-GROUPS AFFECTED

Age (yr)	Paralytic		Non-paralytic	
	Male	Female	Male	Female
1-2	1	1		1
3	2	1	1	2
4	3		2	2
5-9	8	4	2	1
10-14				2
15-24	1			1
25 or more	2	1		2
Total	17	7	5	11

So far as it is possible to ascertain, there had never been a notified case of poliomyelitis in Brightlingsea until the autumn of 1952, when 2 patients with paralytic poliomyelitis were admitted to hospital In the autumn of 1954 8 patients with non-paralytic and 6 with paralytic poliomyelitis were admitted to hospital In October, 1955, 6 cases of non-paralytic poliomyelitis were notified, and from the records it appears that none of these patients was admitted to hospital At that time, however, there were several cases of aseptic meningitis in the surrounding districts, therefore, although the diagnosis of these 6 cases must remain in doubt, it is likely that they were cases, not of poliomyelitis, but of aseptic meningitis In January, 1956, a girl, aged 18, who worked out of Brightlingsea contracted paralytic poliomyelitis No other cases were notified during the year

At the end of January, 1957, a boy, aged $4^1/_2$ years, with symptoms suggesting poliomyelitis, was seen by his general practitioner and was subsequently admitted to hospital and diagnosed as having paralytic poliomyelitis No other case of poliomyelitis was known to exist at that time in East Essex The boy's father worked as a porter on a main-line station Neither the boy's father nor his mother had any illness The boy was discharged from hospital on March 14, 1957 On March 16 2 more cases of poliomyelitis were notified, and from then until the beginning of June there were 37 further confirmed cases

The Brightlingsea epidemic was the first phase of a widespread outbreak of poliomyelitis which later extended north-west to Colchester and the surrounding villages Some centres of population to the east had very few cases, and one centre escaped the epidemic entirely The average incidence in the areas affected was rather more than 1 case per 1000 population—much lower than the 1% incidence in Brightlingsea

Investigations

All the patients were admitted to the infectious-disease unit of the Colchester Group Hospitals Lumbar puncture was done on nearly all the patients, and stools and samples of blood were taken and sent for examination to Dr P Martin at the Public Health Laboratory, Ipswich Samples of stool from some of the contacts were also submitted for isolation of virus Each family in which a case of poliomyelitis had occurred was visited, and a careful history was taken Serological investigations were made at the Virus Reference Laboratory, Colindale, and the results of these investigations are reported in an accompanying article (Boissard 1958)

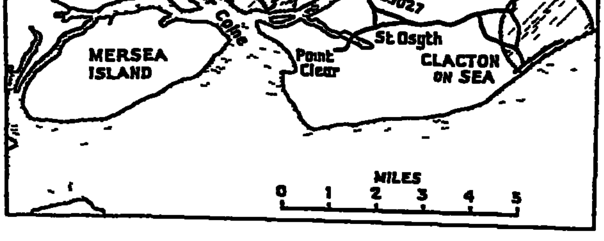
Clinical Findings

Nearly all the Brightlingsea patients complained of frontal headache. They had pyrexia (99–103°F), slight stiffness of the neck, and fairly severe stiffness of the lower two-thirds of the back. In about half the cases the hamstrings felt tight Of the 40 patients 28 had a definite history of an "invasion" stage, with pyrexia, headache, and coryza, before the onset of meningeal symptoms and signs The interval between this "invasion" stage and the onset of meningism varied from a few hours to several days

24 cases were paralytic, most of them showing only slight or moderate muscle weakness Only 3 patients needed subsequent treatment as inpatients of an orthopædic hospital This is partly attributable to the mildness of many cases, but is also due to the fact that a particularly good physiotherapy service exists in the infectious-disease unit to which they were originally admitted

Isolation of Virus

When this outbreak began, it was fortunate that I had been discussing with Dr Martin, director of Ipswich Public Health Laboratory, the possibility of isolating the virus from the fæces of persons with poliomyelitis Subsequently, with his cooperation, Dr P J Wormald,



Topographical relations of Brightlingsea.

of the Cambridge Public Health Laboratory, isolated type-1 virus from 13 of the cases in this outbreak No virus was isolated from the stools of the 6 contacts which were submitted for examination

Spread of Poliomyelitis

An impressive fact at the start of the outbreak was the apparent association of some of the patients (table II) Cases 2, 4, 5, and 6 all lived within a short distance of each other and played together out of school Case 3 had associated with case 2 at school, and case 9 was the mother of case 3 No evidence was obtained of spread of the disease by food or by water, the spread seemed to be either by droplet infection or by fæces The "narrow stream" spread of poliomyelitis seemed to continue throughout the outbreak

The following probable chains of spread are interesting

Chain A —Case 4 (onset March 17) probably infected case 6 (onset March 22) They played together out of school but attended different schools Case 13 (onset March 31) played regularly with cases 4 and 6 Case 30 (onset April 14) was the father of case 13, and case 35 (onset April 19) was the married sister of case 30 and was alleged to have been in contact with cases 13 and 30 Case 20 (onset April 5) also played with case 6, who lives opposite Case 23 (onset April 7) was the sister of case 4 (onset March 17) and had been kept in home and garden quarantine since her sister's illness Case 14 (onset April 1) had been in contact with case 4 at school

It is possible to lengthen chain A Case 2 (onset March 11) was the neighbour and playmate of case 4 Complement fixation tests indicated that case 2 had type-1 poliomyelitis Case 5 (onset March 18) was the father of case 2 The complement-fixation tests again indicated a type-1 infection, but type-2 virus was isolated from the stools It is for this latter reason that these 2 cases are not included in chain A

Chain B —Case 12 (onset March 31) played regularly with case 19 (onset April 4) Case 19 was isolated from March 31 Case 22 (onset April 7) was the aunt of case 12 and was in contact with him on March 24 and 31

In 1956 I vaccinated 13 children in Brightlingsea against poliomyelitis None of these children had symptoms of poliomyelitis, although several of them were very close contacts of confirmed cases of poliomyelitis Furthermore, in each of nine families concerned there were 2 cases of clinical poliomyelitis

Incubation Period

The communicability of poliomyelitis appears to be greatest during the latter part of the incubation period and the onset of symptoms An attempt was made to calculate the probable shortest incubation period in some of the cases For the purpose of this calculation the onset of the invasion phase of the illness was taken as the onset

TABLE II—ANALYSIS OF CASES

Case no	Age (yr)	Sex	Type of poliomyelitis	Onset (1957)	Admission to hospital (1957)	Shortest possible incubation (days)	Remarks
1	4	M	Paralytic	Jan 28	Feb 5		No contact established
2	6	M	„	March 11	March 11		No contact established, attended infants' school, C F T suggested type-1 virus
3	6	M	„	„ 15	„ 15		Attended same school as cases 2 and 4, C F T suggested type-1 virus
4	7	F	„	„ 17	„ 19		Attended same school as cases 2 and 3, neighbour and close contact of case 2
5	33	M	„	„ 18	„ 19	7	Father of case 2, type-2 virus isolated from stools, C F T suggested type-1 virus
6	9	F	„	„ 22	„ 26	6	Contact of case 4 regularly until March 16, type-1 virus isolated from stool
7	$3^{10}/_{12}$	M	„	„ 25	April 1		No known contact, type-1 virus isolated from stool
8	3	F	Non-paralytic	„ 25	„ 2		Close companion of case 7, probably infected from same unknown source, type-1 virus isolated from stool
9	29	F	Paralytic	„ 27	„ 6	12	Contact (mother) of case 3
10	20	M	„	„ 28	March 28		No established contact, cubmaster and Sunday school teacher
11	5	F	„	„ 31	„ 31		No known contact, attended Sunday-school, attended infants' school until March 22, kept away by mother as precautionary measure only, type-1 virus isolated from stools
12	3	M	„	„ 31	April 3		No known contact
13	$6^{10}/_{12}$	M	„	„ 31	„ 8		Played with cases 4 and 6, attended school for four days after start of invasion period April 5–8, type-1 virus isolated from stools
14	6	M	„	April 1	„ 1		Attended infants' school, had played with case 4 at school, type I virus isolated from stool
15	4	M	Non-paralytic	„ 1	„ 3		Had played a week previously with child X, who had been ill with vague pyrexial illness
16	$4^{1}/_{2}$	M	Paralytic	„ 2	„ 3		Contact of case 15 and X
17	$4^{1}/_{2}$	F	Non-paralytic	„ 2	„ 3		No definite contact
18	6	F	„	„ 4	„ 8		Attended infants' school until April 4, contact of case 3 in school twenty days before and of X fourteen days before
19	4	M	Paralytic	„ 4	„ 8	5	Played regularly with case 12 until March 30, no contact with other children whatever
20	$8^{1}/_{2}$	M	„	„ 5	„ 6	14	Played with case 6, who lived opposite, until March 22, attended junior school, type-1 virus isolated from stool
21	3	M	Non-paralytic	„ 6	„ 8		Indefinite contact of case 12, type-1 virus isolated from stool
22	33	F	„	„ 7	„ 7	7	Aunt of case 12, had been in contact seven and fourteen days before onset
23	13	F	„	„ 7	„ 11	18	Sister and contact of case 4, had been isolated at home and in garden since March 17 (onset of case 4)
24	7	F	Paralytic	„ 7	„ 13		Attended infants school, in contact with X and in contact with case 18 before March 29
25	4	M	Non-paralytic	„ 7	„ 14		Contact and neighbour of case 21, type-1 virus isolated from stool
26	$^{10}/_{12}$	F	„	„ 7	„ 14		Sister of case 25 and contact of case 21, type-1 virus isolated from stool
27	3	F	Paralytic	„ 8	„ 8	15	Played each day with case 8, most likely contact, last played on March 24
28	4	F	Non-paraltyic	„ 10	„ 13		Sister of case 24, type-1 virus isolated from stool
29	3	F	„	„ 14	„ 17		No known contact
30	36	M	Paralytic	„ 14	„ 18	14	Father of case 13
31	9	M	„	„ 14	„ 21	10	Regular playmate of case 18 and her brother (case 33), type-1 virus isolated from stool
32	$16^{3}/_{4}$	F	Non paralytic	„ 15	„ 15		Teacher at Sunday school, no other contact
33	9	M	Paralytic	„ 15	„ 15	7	In regular contact with case 18 (sister) until April 8, type-1 virus isolated from stool
34	$^{11}/_{12}$	M	„	„ 18	„ 22	4	Brother of case 31, no other contact known
35	42	F	Non-paralytic	„ 19	„ 20		Sister of case 30 and aunt of case 13, in contact regularly with each
36	6	M	„	„ 22	„ 22		Neighbour and contact of case 24 and playmate of case 33, attended infants' school
37	5	M	„	„ 23	„ 23		No known contact, had been kept away from infants' school for three weeks before April 9, unknown illness in children next door
38	$^{11}/_{12}$	F	Paralytic	„ 26	„ 29		Sister of case 37
39	12	F	Non-paralytic	May 4	May 9	11	Last attended secondary school on April 9, neighbour and playmate of case 37
40	5	M	Paralytic	June 4	June 4		Father a schoolmaster, no contact known

ing (N) antibody Case 13, from whom type-1 poliovirus was isolated in the Cambridge Public Health Laboratory, had paralytic poliomyelitis, but his sister (case 18) and the 4 other children with type-1 N antibody were not known to have had poliomyelitis Table II shows that 5 of the 6 sera with type-1 N antibody also fixed complement with type-1 virus

Type-2 antibody—Only case 17's serum (table I) neutralised the test dose of type-2 virus at 1/32 dilution None of these sera fixed complement with type-2 virus at 1/4 dilution (table II)

TABLE II—RECIPROCALS OF COMPLEMENT-FIXING ANTIBODIES TO THREE POLIOMYELITIS VIRUSES

Vaccinated children				Unvaccinated children			
Case no	Poliomyelitis virus			Case no	Poliomyelitis virus		
	Type 1	Type 2	Type 3		Type 1	Type 2	Type 3
1	<4	<4	<4	10	<4	<4	<4
2	>64	16	64	11	>16<32	<4	>4<8
3	<4	<4	>8<16	12	16	<4	<4
4	>4<8	<4	<4	13	>8<16	<4	<4
5	8	<4	<4	14	<4	<4	<4
6	>16<32	4	>32<64	15	<4	<4	<4
7	>16<32	>4<8	8	16	16	<4	<4
8	32	16	<4	17	<4	<4	<4
9	>16<32	4	>8<16	18	32	<4	<4

Type-3 antibody—No serum neutralised the test dose of type-3 virus at the lowest dilution tested, but table II shows that case 11's serum contained heterologous C F antibody to type-3 virus

These serological results indicate that infection by type-2 and type-3 viruses had not been hitherto widespread in this community

Sera of Vaccinated Children

Type-1 antibody—Table I shows that cases 1 and 3 had serum N antibody commensurate with the level of type-1 antibody found a year after two doses of vaccine (Medical Research Council 1957b) These two sera did not fix complement with type-1 virus (table II), and the findings suggest that these 2 children escaped infection during the epidemic The type-1 N antibody titres of the 7 other sera were higher than might be expected a year after immunisation, and it appears probable that antibody response had been reinforced in these children by infection with type-1 virus In 4 of these sera the high titres found would be unusual after a primary infection in unimmunised children These 7 sera reacted positively in the C F T (table II), but the C F antibody titre was low in the sera of cases 4 and 5 (see below)

Type-2 antibody—Case 8's serum N antibody titre (table I) of 1/8192 suggests an infection by type-2 virus either before or after immunisation Table II shows that 5 of the 9 sera fixed complement with type-2 virus, a rational explanation being that this was because of heterologous C F antibody produced in response to infection of these children by type-1 virus (Casals et al 1952, Svedmyr et al 1953, Schmidt and Lennette 1956) The lack of heterologous C F antibody in the sera of cases 4 and 5 is discussed below

Type-3 antibody—Sera from cases 5 and 8 did not neutralise the test dose of type-3 virus at 1/8 dilution, and at 1/2 dilution when subsequently retested Case 6's serum N antibody was of the order of a secondary response, irrespective of whether primary immunisation or infection occurred first In case 3's serum (table I) type-1 and type-2 N antibodies were within the range of titres found a year after two doses of vaccine, but her serum type-3 N antibody was at the uppermost limit of the observed range (Medical Research Council 1957b) Since this serum gave fixation with type-3 virus in the C F T, there is reasonable evidence that case 3 had been infected by this virus, possibly within the preceding year It is known that type-3 virus was introduced into the area during the epidemic (J A Dudgeon, personal communication) Of the 5 sera which gave heterologous C F reactions with type-2 virus 4 gave heterologous C F reactions with type-3 virus (table II) The fact that case 8's serum did not react in this way with type-3 virus, although fixing complement with type-2 virus, is similar to the observation of Svedmyr et al (1953) that convalescent sera may fix complement with sometimes one and sometimes both of the heterologous viruses The sera of cases 4 and 5 showed no heterologous C F antibody to type-3 virus

Discussion

There were striking similarities and differences in both N and C F antibodies in the sera of these two small groups of children differing only, so far as could be ascertained, in their vaccination status Both groups showed serological evidence of infection by type-1 poliovirus—7 of the vaccinated children against 6 of the unvaccinated children—yet all but one of these infections were subclinical

It is clear that, in some of the vaccinated children, natural infection had had a similar effect on N antibody to that of a third or reinforcing dose of poliomyelitis vaccine In contrast to the unvaccinated children, most of the vaccinated children's sera had all three types of N antibody in high titre a year after they had received two doses of poliomyelitis vaccine

Since these sera were collected four months after the April peak of the epidemic, no evidence can be adduced about transitory heterotypic type-2 antibody (Casals et al 1952, Sabin 1952)

The culture-medium control, which is known to fix complement with very few human sera in the absence of any anticomplementary effect, gave no indication that non-specific C F reactions occurred between the test sera and monkey-kidney cell antigens or other constituents

Table II shows that there were more monotypic C F reactions in the sera of the unvaccinated children than in the sera of the immunised group Since the two groups of children were of similar age, this difference in serological response must be ascribed to immunisation with poliomyelitis vaccine This immunotherapy presumably had caused heterologous C F antibody to appear in the sera of those children who had experienced either an earlier or a subsequent subclinical poliovirus infection Black and Melnick (1954) noted a similar phenomenon in a group of 30 persons tested for N and C F antibodies before and after inoculation with a formalin-inactivated type-1 virus None had C F antibodies before inoculation The C F response was confined almost entirely to those persons and those types where there was pre-existing N antibody

Case 11's serum contained heterologous C F antibody to type-3 virus in the absence of N antibody at 1/8 dilution of serum Similar observations were made by Melnick (1955) and Hammon et al (1955) Attention was directed by Mayer (1955) to possible reasons for cross-C F reactions

Laboratory, for their cooperation, and *Mr James Colvin*, the surveyor and public health inspector of Brightlingsea, who assisted me so ably in these investigations during the outbreak

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ANTIBODIES AGAINST POLIOVIRUS IN VACCINATED AND UNVACCINATED CHILDREN IN AN EPIDEMIC AREA

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M B Lond, Dip Bact
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An epidemic caused by type-1 poliovirus broke out in Brightlingsea, Essex, in the first half of 1957 (Pearce 1958) In a population of 4500 there were notified 46 cases, of which 40 were later confirmed as poliomyelitis

13 children in Brightlingsea had each received two doses of poliomyelitis vaccine on May 17 and June 13, 1956 The high clinical attack-rate in Brightlingsea in April, 1957, prompted a comparative antibody study of small groups of vaccinated and unvaccinated children A single sample of blood was obtained from each child on July 4, 1957 Except for 1 unvaccinated child, both groups consisted of children who had not been ill It was of particular interest to determine, if possible, whether infection with poliomyelitis virus after immunisation would cause heterologous complement-fixing (C F) antibodies to appear The children were selected as follows

The names of unvaccinated children, aged 3–9 years, on the birth registry in Brightlingsea were arranged in alphabetical order and numbered 1–138 60 of these, consisting of 26 boys and 34 girls, were similar in age to the vaccinated group, and 12 of them were paired with 12 of the vaccinated children according to sex by using random numbers Of the 9 vaccinated and 9 unvaccinated children allowed to take part 6 pairs turned out to have been randomised for age and sex as described, since 3 unvaccinated half-pairs who defaulted were replaced by 3 unvaccinated children who were not randomised alternatives for those particular vaccinated children

Methods

Tissue cultures for neutralisation tests—Six-day cultures of monkey-kidney cells were maintained on 1 ml of Eagle's (1955) medium, with added 2 0% of inhibitor-free inactivated horse-serum and 0 1% sodium bicarbonate The inoculum used for each culture in titrations was 0 1 ml of virus or of virus-serum mixture All the test-serum, control-serum, and control-virus titrations were done on one batch of tissue cultures Fluid from cultures showing degeneration of doubtful origin was subinoculated on the sixth day after inoculation This was done in 29 of 742 of the cultures used (3 9%)

Virus suspensions—The strains used in neutralisation (N) and in complement-fixation tests (C F T) were type-1 Mahoney, type-2 MEF-1, and type-3 Saukett These were grown in monolayer cultures of monkey-kidney cells maintained on Mixture 199 (Morgan et al 1950) The harvested culture fluids were centrifuged at 5000 r p m for an hour at +4°C, and the pooled supernatant fluid of each type was distributed and stored at this temperature

Virus titrations—Suspensions were diluted in tenfold steps with Mixture 199 containing 0 1% bicarbonate Four tissue cultures were inoculated with each dilution of virus Geometric mean titres were $10^{-6\,0}$, $10^{-5\,7}$, and $10^{-6\,3}$ for virus of types 1, 2, and 3 respectively

Neutralisation by test sera—These were stored at −30°C and were thawed once only before being tested Sera were heated at 60°C for twenty minutes Serial dilutions of each serum in Hanks' solution containing 0 01% sodium bicarbonate were mixed in 0 6 ml volumes with an equal volume of virus suspension to give serum dilutions of 1/8–1/4096 in fourfold steps and an estimated challenge dose of 100 TCID_{50} per 0 1 ml of inoculum of each virus type After being shaken the serum-virus mixtures were placed at 37°C in an air incubator for three and a half hours (Medical Research Council 1957a) before inoculation of two tissue cultures with each dilution

Neutralisation by control sera—British Standard poliomyelitis monkey antisera from the department of biological standards, Mill Hill, were hydrated as directed Serial dilutions of each serum were mixed in 1 ml volumes with an equal volume of each virus suspension used in the test, to give control serum dilutions from 1/40 to 1/320 in twofold steps These were then treated like the test sera, except that four tissue cultures were inoculated with each dilution

Complement-fixation test—The method of Fulton and Dumbell (1949) was used in straight-line tests as described by Le Bouvier (1953) The optimum concentrations of the live virus suspensions which served as antigens in the test were 1/2 for Mahoney and Saukett, MEF-1 was used as the undiluted suspension Two exact units of complement were added in the test, the unit being defined as the highest dilution of complement which, when titrated in the presence of each virus suspension under the conditions of the test, caused 50% hæmolysis of the maximally sensitised sheep red cells Serum dilutions in barbitone buffer were screened at initial dilutions of 1/4–1/64 in twofold steps Serum controls, virus and culture-medium controls, and hæmolysis controls were included in the test

Results

Control Sera

The neutralising titres obtained in the test were 1/160, 1/190, and 1/280 for type 1, 2, and 3 sera respectively The geometric mean titres for the British Standard poliomyelitis sera are published as 1/480, 1/806, and 1/960 for type 1, 2, and 3 sera respectively (Medical Research Council 1957a), but in the M R C tests five times greater volumes of each serum were used In table I the reciprocals of the neutralising antibody titres of the test sera have been multiplied by the ratios 3, 4, and 3¹/₂ for types 1, 2, and 3 respectively, to facilitate comparison of these results with those published by the Medical Research Council (1957b) on the antigenic activity of British poliomyelitis vaccine in children

Sera of Unvaccinated Children

Type-1 antibody—Table I shows that of the 9 sera, 6 had type-1, 1 had type-2, and none had type-3 neutralis-

TABLE I—RECIPROCALS OF SERUM DILUTIONS (IN SERUM-VIRUS MIXTURES) WHICH NEUTRALISE 100 TCID_{50} OF EACH POLIOVIRUS TYPE
(Sera of vaccinated and unvaccinated children collected July 4, 1957)

Children vaccinated in May and June, 1956						Unvaccinated children registered in 1956					
Case no	Age (yr)	Sex	Poliomyelitis antibody			Case no	Age (yr)	Sex	Poliomyelitis antibody		
			Type 1	Type 2	Type 3				Type 1	Type 2	Type 3
1*	$3^{6}/_{12}$	F	<32†	2048	112	10*	4	F	<8	<8	<8
2*	$5^{8}/_{12}$	M	12,288	1024	896	11*	6	M	3072	<8	<8
3*	$6^{8}/_{12}$	F	24	512	3584	12*	7	F	3072	<8	<8
4*	$6^{6}/_{12}$	M	6144	2048	56	13*	$6^{7}/_{12}$	M	1536	<8	<8
5*	$5^{4}/_{12}$	F	12,288	512	<8	14*	$5^{6}/_{12}$	F	<8	<8	<8
6*	$5^{6}/_{12}$	F	6144	512	14,336	15*	$6^{4}/_{12}$	F	<8	<8	<8
7	$6^{6}/_{12}$	F	3072	4096	<32†	16	$5^{6}/_{12}$	F	1536	<8	<8
8	$3^{8}/_{12}$	M	1536	8192	<8	17	$5^{5}/_{12}$	F	384	32	<8
9	$4^{4}/_{12}$	M	3072	1024	1792	18	$4^{11}/_{12}$	F	1536	<8	<8

* Vaccinated and unvaccinated pairs randomised for age and sex
† Dilution at 8 not tested

ing (N) antibody Case 13, from whom type-1 poliovirus was isolated in the Cambridge Public Health Laboratory, had paralytic poliomyelitis, but his sister (case 18) and the 4 other children with type-1 N antibody were not known to have had poliomyelitis Table II shows that 5 of the 6 sera with type-1 N antibody also fixed complement with type-1 virus

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5	8	<4	<4	14	<4	<4	<4
6	>16<32	4	>32<64	15	<4	<4	<4
7	>16<32	>4<8	8	16	16	<4	<4
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Type-3 antibody—No serum neutralised the test dose of type-3 virus at the lowest dilution tested, but table II shows that case 11's serum contained heterologous C F antibody to type-3 virus

These serological results indicate that infection by type-2 and type-3 viruses had not been hitherto widespread in this community

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Since these sera were collected four months after the April peak of the epidemic, no evidence can be adduced about transitory heterotypic type-2 antibody (Casals et al 1952, Sabin 1952)

The culture-medium control, which is known to fix complement with very few human sera in the absence of any anticomplementary effect, gave no indication that non-specific C F reactions occurred between the test sera and monkey-kidney cell antigens or other constituents

Table II shows that there were more monotypic C.F reactions in the sera of the unvaccinated children than in the sera of the immunised group Since the two groups of children were of similar age, this difference in serological response must be ascribed to immunisation with poliomyelitis vaccine This immunotherapy presumably had caused heterologous C F antibody to appear in the sera of those children who had experienced either an earlier or a subsequent subclinical poliovirus infection Black and Melnick (1954) noted a similar phenomenon in a group of 30 persons tested for N and C.F antibodies before and after inoculation with a formalin-inactivated type-1 virus None had C F antibodies before inoculation The C.F response was confined almost entirely to those persons and those types where there was pre-existing N antibody

Case 11's serum contained heterologous C.F antibody to type-3 virus in the absence of N antibody at 1/8 dilution of serum Similar observations were made by Melnick (1955) and Hammon et al (1955) Attention was directed by Mayer (1955) to possible reasons for cross-C F reactions between the three poliomyelitis viruses when unpurified concentrated virus suspensions are used Mayer et al (1957) have shown that highly purified suspensions of the three viruses have type-specific C F reactions with human convalescent sera

Of the vaccinated children, case 1's serum showed no complement fixation with any poliovirus With the test in use here it has been found that primary immunisation with two doses of vaccine does not appear to give rise to detectable levels of C F antibody in the absence of diagnosed infection Exceptions do occur, but in such persons it has been impossible to rule out antecedent subclinical infection Some recent tests in collaboration with Dr J O'H Tobin and Dr A D Macrae have shown that a third dose of vaccine is generally followed by the appearance of all three types of C F antibody How long these C F antibodies persist is not yet known

When suspensions of unheated live virus are used as antigens in the poliomyelitis C F T, homologous C F antibody often appears slowly in the sera of persons who have not before been infected by any poliomyelitis virus (Black and Melnick 1954, Le Bouvier 1955, Schmidt and Lennette 1956) The development of heterologous C F antibodies annuls the diagnostic value of a single convalescent specimen of serum, but, because of their rapid appearance, a rise in titre of homologous C F antibody can be demonstrated in a substantial proportion of cases, in felicitously spaced sera, when suitable virus suspensions are used (Schmidt and Lennette 1956)

The problem is of practical importance, now that widespread immunisation of children is being practised The evidence presented suggests that primary immunisation increases the frequency with which heterologous C F antibodies appear in such children's sera when they are infected by a poliovirus

C F antibodies decrease in time and may become undetectable after a few months (Lennette and Schmidt 1957) Heterologous C F antibody tends to wane even more rapidly Since the date of infection is not known for any of the children investigated, it is possible that the low homologous C F antibody titres of the sera of cases 4, 5, and 17, as well as the absence of heterologous C F antibody from the sera of cases 3–5, are a result of such antibody decline

Conclusions

This small-scale investigation calls for suggestions rather than assertions, but there is some evidence that

(1) Infection superimposed on primary poliomyelitis immunisation causes in some children a N-antibody response to the infecting virus, similar to that of a third dose of vaccine

(2) It is essential to obtain paired sera from immunised children when investigation by the C F technique for poliomyelitis is required

(3) The C F T is still of value in the diagnosis of poliomyelitis infections in children who have received two doses of vaccine, but recent tests on sera obtained a *fortnight* after a third dose of vaccine suggest that the C F T may be of little or no value in diagnosing subclinical poliomyelitis infections during this period

Summary

Serological tests for neutralising and complement-fixing antibodies were made on two small similar groups of children one group had received two doses of poliomyelitis vaccine in 1956, and the other group had been registered but was not yet vaccinated

The investigation was made a few months after a poliomyelitis epidemic in 1957

In children who already have been immunised with two doses of vaccine the C F T for poliomyelitis may be of diagnostic value, but only when paired sera are examined

Recent tests made on sera taken a fortnight after a third dose of vaccine indicate that the C F T will be of little or no diagnostic value during this period

Infection a year after immunisation with two doses of vaccine causes in some children an N-antibody response to the infecting virus, similar to that of a third dose of vaccine

I wish to thank Dr J D Kershaw, area medical officer for North East Essex, and Dr Eleanor Singer, assistant county medical officer of health, for their help, Dr R D Pearce, medical officer of health for Brightlingsea, and his staff, without whose cooperation this investigation would not have been possible, Dr W C Cockburn, director, Central Public Health Laboratory, Dr F O MacCallum, director, Virus Reference Laboratory, and Dr C C Spicer, who randomised the registered children

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International Requirements for Poliomyelitis Vaccine

International requirements for the production and control of the Salk type of poliomyelitis vaccine have been formulated by a group of experts meeting recently in Geneva under the auspices of the World Health Organisation and the chairmanship of Dr J H S Gear In the past difficulties have often been put in the way of the free exchange of vaccine because of differences in the manufacturing and control methods applied in the country of origin and in the country wishing to use the vaccine When finally accepted, the new requirements are expected both to *facilitate the international exchange* of vaccine and to *provide guidance* and assistance to countries wishing to start production and control of vaccine This is particularly important now because in many countries where poliomyelitis was formerly rare, there have been severe epidemics in recent years

Other biological substances such as yellow-fever and cholera vaccine, blood and plasma, will be the subjects of similar recommendations for production and control requirements to be formulated by other W H O study groups during the coming *months This work is a new development in one* of W H.O 's most important programmes, that of biological standardisation In cooperation with more than 100 laboratories in different parts of the world, W H O has so far established about 50 new biological standard preparations, ranging from diphtheria antitoxin to a whole series of antibiotics This has made it possible for these substances to be measured and described in terms of international units accepted throughout the world

Special Articles

"CALLING DR. KILDARE"

STAFF-LOCATION SYSTEMS SUITABLE FOR HOSPITAL USE

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WESTERN REGIONAL HOSPITAL BOARD, GLASGOW

IN a large hospital much of the work is done with the help of the telephone. An efficient communication system is an important part of the structure and one which is seldom provided. Existing installations in many hospitals are unsatisfactory for the following reasons

(1) At certain times of the day the switchboard becomes overloaded and no lines are available for incoming or outgoing calls

(2) Even when lines are available, the switchboard operators are often so busy that there is delay in dealing with calls

(3) Much time is wasted in finding members of the staff required for a telephone call Nurses and other skilled people are often used as messengers

(4) Telephone bells make an unwelcome noise in the wards

Staff-location Systems

One of the principal defects in existing hospital communications is the lack of a satisfactory method of finding an individual and bringing him to the telephone to answer an incoming call The staff of a large hospital may include 50–100 people who are often sought for this purpose, on many occasions only one person is competent to deal with a particular inquiry or request. The problem of finding an individual, who may be anywhere in a large building, without disturbing anyone else, is technically difficult and until recently has never been satisfactorily solved

A study of this matter was begun in the Regional Physics Department in 1953 at the suggestion of Prof C. F W Illingworth The first step was to write an outline specification of the equipment required The ideal characteristics for a staff-location system were decided to be the following-

(1) It should be silent

(2) It should attract the attention of the individual who is being sought but not of anyone else

(3) It should operate at every point in the building

(4) It should not require any attention or concentration on the part of the staff who use it.

No conventional telephone installation will meet these requirements, nor will any system of loudspeakers or coloured lights Consideration was therefore given to the possibility of pocket receivers, each tuned to a particular frequency and actuated by signals under the control of the telephone-switchboard operator Such a system appeared technically feasible, and inquiries were made of several manufacturers A voluminous correspondence ensued, but by the middle of 1955 it was apparent that none of the firms approached was in a position to do what was required

Towards the end of 1955 it was learnt that two firms, Multitone Electric Co Ltd. and British Communications Corporation Ltd, were engaged in developing staff-location systems answering to the specification outlined above, using the magnetic induction method This is a simple and surprisingly effective way of transmitting signals to any place inside a building It uses the following apparatus:

(1) A continuous wire attached to the outside of the building and forming a loop

(2) A transmitter connected to the ends of the loop

(3) A control unit placed near the main telephone switchboard.

(4) Pocket receivers using transistors for detection and amplification.

The external wiring is easily done. Aluminium wire about 3 mm in diameter covered with a 1-mm layer of polyvinyl chloride is a suitable material, being cheap and durable For a six-storey building of 19th-century construction a single loop at second-floor level will often be adequate For more modern buildings, containing a lot of structural steelwork, subsidiary loops may be necessary to eliminate dead spots inside It is usually convenient to fix the wire to the outside walls with staples every few yards but it can equally well be attached to the skirting boards or the inside walls

The transmitter is an electronic device generating alternating current at several frequencies one for each receiver. Once installed the transmitter needs little attention

The control unit is a small box with switches or push-buttons corresponding to the various frequencies obtainable from the transmitter

Each receiver is tuned to a particular frequency By pressing one key on the control unit the switchboard operator sends through the loop a signal which will be detected by only one receiver The normal practice is to transmit a buzzer signal, which advises the recipient to go to the nearest telephone to take an incoming call Facilities for speech transmission are also available but they are not likely to be of much use in a hospital Two-way communication is not yet possible

The following systems are now being made in Britain

Multitone Staff-Location System (Multitone Electric Co Ltd., 12–20 Underwood Street London N 1) installed at St Thomas's Hospital, Westminster Hospital St George's Hospital, Manchester Royal Infirmary &c

Radiopage (British Communications Corporation Ltd Exhibition Grounds. Wembley) installed at Western Infirmary Glasgow Royal Mental Hospital Glasgow, The London Hospital. &c.

Selectacall (Westrex Co Ltd Liberty House Regent Street London, W 1) installed at Duchess of York Hospital for Babies Manchester

Another system using V H F radio transmission instead of magnetic induction, has been announced but not yet installed in a hospital

Page Boy (Cotterill-Ginn Ltd, 13 Suffolk Street. London, S W 1) Signals are transmitted from suitably placed radiators, each containing a small oscillator and an aerial The radiators are connected to the control unit by lead-covered cable. no loop is placed round the building

Further details of these systems are given in the table

Other manufacturers are known to be developing staff-location systems, but details are not available.

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* Now with J and P Coats Ltd., Paisley

DETAILS OF STAFF-LOCATION SYSTEM

—	Multitone	Radiopage	Selectacall	Page Boy
Size of receiver (cm)	14×3	19×7×2	13×5×2	15 0×7 0×2 5
Mass of receiver (g)	140	225	150	175
No of separate frequency channels *	36 or 56 (different models)	50	50 or 100 (different models)	141
Frequency band used by transmitter	2–15 kc/s	75–87 kc/s	155 kc/s	465 mc/s
Method of frequency selection	Tuned circuit in receiver	Crystal-controlled filter in receiver	Tuned reeds in receiver	Tuned circuit in receiver
Power supply for receiver	Mercury battery	Mercury battery	Hearing-aid battery	Rechargeable battery
Estimated life (wk)	8–10	10–12	7–8	
Cost of battery	*2s 6d*	*7s 6d*	*3d*	
Cost of transmitter and control unit	From £125 †	£475	£225 †	§
Cost of each receiver	From £18 18*s* †	£25	£24 †	£21 15*s*
Nature of signal	Buzzer ‡	Buzzer and speech	Buzzer	Buzzer ‡

* It is often convenient to extend the capacity of the system by allocating the same frequency to two or more receivers, using a simple code to provide separate calling signals

† Also available on ten-year lease, with quarterly rental

‡ Speech signal also available by pressing switch and holding receiver to ear in response to special calling tone

§ Modulator unit £52 10*s* Radiators each £11 5*s* The number required will depend on the size and shape of the building A typical 500-bed hospital would probably use at least 20 radiators Battery chargers £25 10*s* for every 12 receivers

Post Office Licence —Each of these systems requires a special licence from the Post Office, at a charge of £2 for five years

Trial and Results

A practical trial of a magnetic-induction system was made during 1956 and 1957 at the Western Infirmary of Glasgow The external wiring of the building was completed, with contractor's labour, at a cost of under £300 A complete set of equipment was supplied on loan by the manufacturers A research assistant (H C E) spent about six months collecting data before and after the installation of the personal calling system

EXISTING TELEPHONE INSTALLATION

The Western Infirmary has two main telephone systems

(1) A Post Office installation consisting of a two-position switchboard with 17 exchange lines (of which 7 are available for outgoing calls only) To this switchboard 118 extension telephones are connected

(2) A private automatic exchange for internal calls only, with 123 extension telephones There are smaller installations in various departments of the hospital

A survey made by the Post Office telephone department showed that the number of exchange lines provided for the hospital was about right for the volume of traffic, but that a larger switchboard, with more operators, was necessary for an efficient service at peak hours

Telephone Traffic Handled by Switchboard

During the busy periods (from 9 A M to noon and from 2 P M to 5 P M) in one week a note was made of the destination of each call passing through the switchboard to a ward, department, or individual in the hospital Some of these calls originated outside the hospital and some inside, calls passing out of the hospital were not recorded Of the 1700 calls noted in this way 44% were for wards, 44% for departments, and 12% for named individuals

Telephone Traffic in Ward Corridor

Observations were made on 200 incoming calls to a busy surgical unit Of these 200 calls, 107 were inquiries about the progress of patients, usually from relatives or from doctors outside the hospital Of the remaining 93 calls, 46 were for members of the medical staff of the unit In 19 instances the person sought was found in the unit, with an average delay of 1 5 minutes In 27 instances the person sought was not found in the unit the average time elapsing before this information was given to the caller was 1 7 minutes

In this small sample 41% of the doctors sought were found in their own units A similar inquiry covering other parts of the hospital gave a result not significantly different of 100 incoming calls to switchboard for named individuals the caller was connected at the first extension tried by the operator in 59 cases, at the second extension tried in 27, at the third extension tried in 10, at the fourth extension tried in 2, and at the fifth extension tried in 1 case 1 caller rang off before the connection was made

Waiting-time and Talking-time

The time occupied by the 200 above-mentioned incoming calls was 335 minutes, consisting of 62 minutes' ringing, 148 minutes' waiting for the person required to reach the telephone, and 125 minutes' talking In other words, of the total time for which telephone circuits were occupied, 19% consisted in waiting for someone to answer the bell, 44% waiting for the person required to come to the telephone (total waiting-time 63%), and 37% of conversation between the caller and the person sought

PERSONAL CALLING SYSTEM

When these inquiries had been completed the personal calling system was installed Fourteen receivers were issued on Nov 5, 1956, and others were gradually put into use up to a total of forty-five, leaving five as a reserve stock to cover breakdowns The control unit was fixed in the switchboard room, and the operators quickly became familiar with their new duties

The allocation of receivers was carefully considered in the knowledge that initial mistakes would not be rectified without difficulty and annoyance After studying the results outlined above it was decided that receivers should be issued to the following groups of staff

(1) *House-officers* in medical, surgical, gynæcological, and casualty units These members of the staff have many responsibilities in the day-to-day conduct of the wards and are often hard to locate This is particularly true on receiving days, when the residents are exceptionally busy and outside calls (about the admission of patients) are many

(2) *Ward sisters* —Half the calls coming to the wards are inquiries about the progress of individual patients When the sister, or her deputy, has a personal receiver in her pocket, such inquiries can be handled very efficiently The switchboard operator, on receiving a call for one of the wards, asks the caller if he is inquiring about a patient If he is, the operator presses a switch on the control panel to transmit a buzzer signal heard by the sister or the nurse for whom it is intended The recipient then goes to the nearest telephone and speaks to the inquirer

(3) *Individual members of the hospital staff*, including the medical superintendent, the matron, the administrative officer, the catering officer, and a few doctors whose duties extend to many parts of the hospital

(4) *Duty anæsthetists*

Impressions of the New System

The issue of personal receivers produced an immediate improvement in the efficiency of the hospital telephone system The following subjective reactions were noted

(1) *Switchboard operators* reported that persons carrying receivers could be located in a fraction of the time normally required

(2) *Practitioners* outside the hospital commented on the speed with which the receiving physicians and surgeons could now be found, in welcome contrast to the long delays previously experienced

(3) *Ward sisters* reported that their corridors had suddenly become quieter Where a full issue of personal receivers has been made, the telephone bell seldom rings, because most of the calls are notified individually to the people concerned, about 75% of the calls coming to a ward unit are intended for either the resident or the sister

Objective Tests

From the information already presented it will be clear that a major source of inefficiency in the telephone system is the long delay before a call is answered by the person sought Any improvement here will materially ease the switchboard operator's burden and will increase the amount of traffic that can be handled at busy periods of the day With these considerations in mind an objective assessment of the calling system was attempted by making surveys of 500 calls for persons carrying receivers, and of 200 calls during the same period for persons not carrying receivers The difference between the numbers of calls studied in these two surveys was due to the fact that, by the time that the observations were made, most of the people likely to receive a lot of calls had been issued with personal receivers Consequently the number of calls for individuals outside the network was relatively small

The significant parameter was judged to be the time required to locate the recipient of the call and bring him to the telephone The result of the comparison was ,

200 calls using ordinary telephone system	average delay 63 seconds
500 calls using personal receivers	average delay 25 seconds

Further analysis showed the following differences

AVERAGE DELAY BEFORE BEGINNING OF REPLY TO CALLER

Type of call	Ordinary telephone (sec.)	Personal calling system (sec.)
Calls for doctors	80	35
Inquiries about patients	54	15

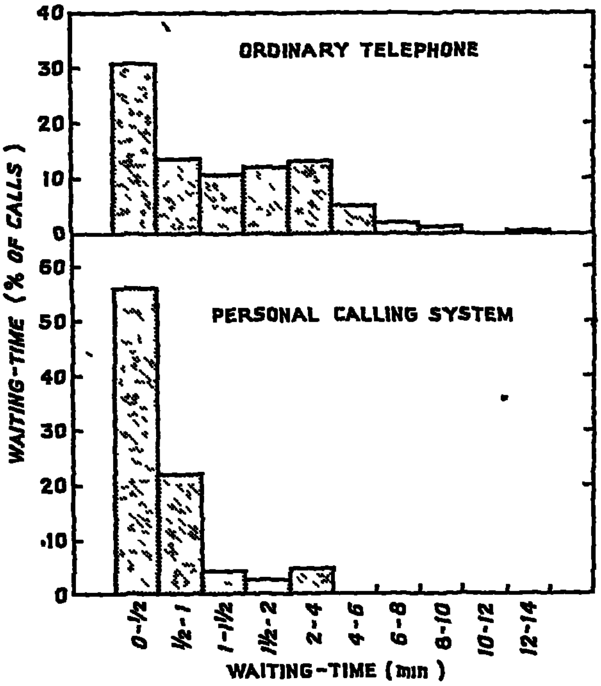
Since the talking-time is not appreciably different whether the call is announced by a personal receiver or by a telephone bell, the following comparison may be made

	Ordinary telephone	*Personal calling system*
Average waiting-time (sec.)	63	25
Average talking-time (sec.)	38	38
Average total time per call (sec.)	101	63

The information collected in these two surveys is displayed graphically in the accompanying figure, which shows that the operators sometimes spent as long as 14 minutes in trying to find a member of the hospital staff for a telephone call When the personal calling system was installed, the operators were advised not to wait longer than 2 minutes for a reply from the person sought This restriction of waiting-time was observed in all but a few instances, when the operators were too busy with other calls Even so, the longest delay before completion of a call or dismissal of the caller was no more than 4 minutes The proportion of calls not completed because the recipient could not be traced was as follows

Personal calling system	56 of 500 calls (11%)
Ordinary telephone	22 of 200 calls (11%)

These figures indicate that everyone responded to the personal-receiver call within the time allowed The residue of 11% presumably represents the proportion of people called who were out of the hospital at the time



Waiting-time in connection with ordinary telephone and with personal calling system

General Observations

Cost—The initial cost of a complete installation may be estimated from the figures given above Other factors, including reliability and ease of maintenance, should also be considered if knowledgeable advice is available The cost of the wiring depends on the system chosen and on the layout of the building Detached blocks can be connected to the main loop by buried cables

Number of receivers needed—Our experience suggests that personal receivers should be issued only to people who will often be required to answer telephone calls and whose duties take them to many different places in the hospital—namely, house-officers and duty anæsthetists, ward sisters, and peripatetic officials (possibly including clerk of works, catering officer, administrative officer, and night sister)

Interference—All the calling systems mentioned here operate at frequencies causing no interference with electroencephalographs, electrocardiographs, and other sensitive equipment likely to be found in a hospital

Before a staff-location system is introduced, the local telephone manager of the Post Office should be asked to report on the condition of the hospital's communication facilities in relation to the traffic handled A further survey should be made in the hospital by an investigator trained in the technique of work study It will often be found that useful improvements can be effected at little or no cost by rearranging the existing installation These inquiries will also provide a basis for administrative decisions on the purchase of a calling system and on the allocation of receivers The cost of the investigations should not exceed £150, even in a very large hospital

Summary

Staff-location systems suitable for use in hospitals have been devised by several manufacturers

Technical features of the equipment now available are described and the results of a practical trial made in a large teaching hospital are reported

The investigation described here was made possible by a grant from the Nuffield Provincial Hospitals Trust on the advice of its Scottish Advisory Committee We are grateful to the board of management for Glasgow Western Hospitals for permission to carry out trials in the Western Infirmary, where we received much assistance from the medical superintendent as well as from members of the medical, nursing and administrative staff We received expert and timely advice on many aspects of the work from Mr W A Gay, of the department of industrial administration, Royal College of Science and Technology, Glasgow, and from members of the Telephone Manager's staff, Glasgow area The apparatus used in the tests was supplied by British Communications Corporation Ltd

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BIRTHDAY HONOURS

The list of honours published on June 12 contains the names of the following members of the medical profession

O M

Sir Macfarlane Burnet, M D Melb, M D, SC D Cantab, F R C P, F R S
Director, Walter and Eliza Hall Institute, Melbourne, professor of experimental medicine, University of Melbourne

K C V O

John Douglas McLaggan, C V O, M B Aberd, F R C S

K B E

Charles Ritchie Burns, O B E, M D N Z, F R C P
Physician and cardiologist, Wellington Hospital, New Zealand

Frederick Horace Smirk, M D Manc, F R C P, F R A C P
Professor of medicine, University of Otago

Knights Bachelor

Brigadier John Smith Knox Boyd, O B E, M D, LL D Glasg, F R C P, F R S
President, Royal Society of Tropical Medicine and Hygiene, formerly director of pathology, War Office, and director of Wellcome Laboratories of Tropical Medicine

Colonel Aldington George Curphey, C B E, M C, E.D, M D Queen's Univ, Canada
President, Legislative Council, Jamaica

John Carew Eccles, M B Melb, M A, D PHIL Oxon, F R A C P, F R S
Professor of physiology, Australian National University, Canberra

Benjamin Thomas Edye, C B E, CH.M Sydney, F R C S, F R A C S
Consulting surgeon, Royal Prince Alfred Hospital, Sydney

Brigadier Kenneth Barron Fraser, C B E, E D, M B Sydney, M S Queensland, F R A C S
Late Australian Military Forces, for public services

Eric William Riches, M C, M S Lond, F R C S
Surgeon and urologist, Middlesex Hospital, London

C B (Military)

Air Vice-Marshal Lancelot Miller Corbet, C B E, M B Melb

Major-General John Huston, M B Belf, F R C S E, Q H S

Surgeon Rear-Admiral Richard Louis Gibbon Proctor, M D Dubl, F R C P I

C B (Civil)

George Edward Godber, D.M Oxon, F R C.P
A deputy chief medical officer, Ministry of Health

C.M.G

James Malcolm Liston, M B Glasg
Director of medical services, Tanganyika

Richard Murchison Morris, O B E, M D Lond
Secretary for Health, Federation of Rhodesia and Nyasaland

C V O

James Crooks, M B Edin, F R C S

C B E (Military)

Colonel Robin Arthur Smart, M B Aberd, R A.M C.

Air Commodore Denis Aymard Wilson, A F C, M R C.S, F F R, Q H S, R A F

C B E (Civil)

Daniel Fowler Cappell, M D Glasg, F R F P S
Professor of pathology, University of Glasgow

Charles Skinner Hallpike, M B Lond, F R.C P, F R C.S, F R.S
Director, Medical Research Council otological research unit, National Hospital, Queen Square, London

Jean MacIver Mackintosh, M D Glasg
Administrative medical officer of health for maternity and child welfare, Birmingham

O B E (Military)

Lieut -Colonel Warren John Boyd, E D, M B, R N Z A M C

Lieut.-Colonel Denis Henry Dryburgh Burbridge, M R C.S, R A M C

Group-Captain Roy Brasmere Davis, M B Melb, R A A F

Wing-Commander Frederick Latham, M D Manc, R A F

O B E (Civil)

Basil George Brooke, M D Dubl
Chairman, Medical Board, Manchester, under the National Service Acts

Alexander Mackay Calder, M B Edin, F R C S E
Surgeon, Newtownards Hospital, Co Down

Herman Robert Frederick, M B Edin
General practitioner, Port Talbot

Ernest Wightman Ginner
Physician, Sunnybank Hospital, Cannes

Stanley Augustine McDonnell, CH M Sydney
For services to the community in the Balonne area, Queensland

Alasdair McKelvie, M B Edin
Lately specialist leprologist, Ghana Ministry of Health

Lily Margaret O'Hanlon, M R C S
Head of Pokhara Mission Hospital, Nepal

Cecily Mary Wise Pickerill, M B N Z
Formerly plastic surgeon, Wellington Hospital, New Zealand

Robert Merrick Lloyd Still, M R C S
Medical superintendent, Mental Hospital, Barbados

Eric Blake Wild, M B Lond, F R C S E
Doctor-in-charge, Church Missionary Hospital, Isfahan

M B E (Military)

Squadron-Leader Charles John Williamson Soutar, M B Lond, R A F

M B E (Civil)

Charles Donald Ferguson, M B Glasg, J P
For political and public services in Ross and Cromarty

Arthur Stephen Garrett, M B Lond
Medical officer, Leprosy Service, Eastern Region, Nigeria

Gavin Muir, M B Glasg
Member, Medical Board, Newcastle, under the National Service Acts

In England Now

A Running Commentary by Peripatetic Correspondents

WHY are we doctors often so unpredictable? Why does our attitude to our patients vary so much according to their environment? Of course I had always realised that a few doctors were inclined to treat their patients in hospital like rather deaf overgrown children, but *I* certainly didn't. However it has been brought home to me very kindly but pretty plainly that perhaps I am no better than the rest.

My patients, two rather charming elderly ladies, had been to see a physician in his consulting-room and were delighted with the way he carried out the examination. In fact we united in saying what a thoroughly nice person he was. But then came the pill in the jam. "Why, doctor," they asked me, "is he so different when you are an inpatient in hospital? He shouts across the ward. He is always in a hurry. His actual treatment is above reproach, but you are no longer a person, you are just a number, and when tackled he admitted it himself." I murmured the usual platitudes and left it at that. But later I remembered that at different times both these old ladies had been in hospital under me, and how had I treated them? Certainly not as I treated them when I visited them at home. I had asked them questions but had looked to the nurses for a reply. I had prescribed treatment but had left it to the Sister to explain what it was meant to do. I had spoken to *them from the foot of the bed. It is* easy enough to say that I find a hospital ward inhibiting, to blame the hospital staff, and feel that they tend to serve the patient up to us rather like a broken piece of machinery which, acting on our instructions, they are endeavouring to clean up, polish, and put in working order. They appear to resent a request to leave us alone with the repaired article, and on busy days it is easier to acquiesce, to talk over the patient's head, to forget that removal from home to hospital has not changed an intelligent person into someone who is unable to hear easily or answer questions.

My patients never hinted that they thought I was at all to blame. They are kinder than their doctor and would not hurt my feelings for anything, but it made me think, and what I thought wasn't exactly pleasant.

* * *

Twenty years ago, the gynæcology in my hospital was done by the general surgeon, because there was no gynæcologist at that time. The theatre nurse was one of the loveliest girls I have ever seen; she was known as "the houseman's heartbreak", and her beauty was equalled by her competence. I was engaged in the removal of two ruptured dermoid cysts, the cyst wall was adherent to both large and small intestine. Finger dissection was impossible, and the precarious process of separating the adhesions at the point of a sharp scalpel was arduous. At last I got the operation successfully completed, and closed the skin, remarking somewhat sententiously to the nurse, "Well, Nurse, *finis coronat opus*, if you know what that means." She replied, "Yes, Sir," and I asked, "Well, what *does* it mean, Nurse?" She answered, "I don't know any Latin, but I suppose it means it looks all right when the skin is closed."

* * *

Maybe I do look a square to the hep cats. Theirs is a hasty judgment. My bathroom mirror would tell a different tale, a more curvaceous profile would be hard to find, if you are not too fussy about segmental distribution. Anyway, a man should carry all before him with a permanent dignity of mien denied to the overpublicised fallout of the film stars, or his more transient competitors in the third trimester of expectant joy. But the hep cats are more scornful of my mind than mere flesh. It is positively indecent that Father should still have a *yen to dig* that crazy rhythm, and frantically pathetic when I try. Five stone and thirty years ago was where I came in, with my Oxford bags boring holes through the ballroom air. The bags are now under my eyes, the fireside chair needs re-springing, but somewhere up in the frontal lobes the old arterioles jive into spasm when the offbeat pulses stir up the past. Skiffle sends me. Sends me back, not only to the sentimental memories of the sweetest music this side of Heaven and the decorous gaiety of swing, but schizophrenically back to the half-lit cellars of Harlem, the throbbing primordial drumbeat, that curious scent, the dime-a-dance magnetic contact with inborn basic rhythm. No, Siree, only the years elbow me out of the groove. But I am fighting back.

As I mushroom over the bar stool, swilling the talc dust from my tonsils, and doing a surreptitious hand jive, I think how unenterprising are the youth of today. Their terminology is so boringly monotonous. If they have chosen to call themselves hep cats, why stop there? There is the whole range of veterinary pathology to give descriptive colour to their convulsions. Encephalomalacia has a pleasant syncopation in its own right, but they could really go to town on its synonym, crazy chick disease. What scope for the pop singer to shriek in his opisthotonos "Dig that crazy rhythm, Chicks, I've crazy chick disease." And the touching euthanasia of his partner's request to be put down forthwith. Strychnine seems to be doing the job quite adequately; cyanide would be too good for some of them.

Localised copper deficiency is just inviting swayback at midnight ballroom orgies. Beware of the hep with hepatitis, foot-stab is the recognised treatment in the best veterinary and chuckerout circles. Foot-and-mouth is the cry for song and dance in the cabaret; foot-rot marks the sitters out. Surely a cysticercus would be a more attractive title than a jam session on a tape recorder, and much more hospitable. If the idea catches on, just think of the vibriosis on the floor, the warble of muted clarinets, the curled tongue trumpeters, the push and pullorum of jiving, the free range, the coolness of the cats. Those kids don't know they're alive yet. Wait till my new diet melts the corners off. I'll show them I'm no square.

* * *

On my last flight home from New York altitude went to my head and British reserve forsook me. There were, of course, extenuating circumstances, for the lady who took the seat beside me was at least 70 years old and travelling alone. Courtesy dictated that I should help her in every way. She had flown in from San Francisco and was going on to Mainz, her home until 1906, her command of the English tongue could hardly have improved since. My respect for her grew as she ordered a manhattan from the stewardess, but there lay my undoing—or was it perhaps the bourbon I had taken myself—for as the stewardess reappeared I offered the second, which to my surprise she accepted. Her tongue was loosened and her life story unfolded. Fifty years a chiropractor! Case-history followed case-history against the tamponade of aero-engines—worse than any surgical meeting. There was the governor of Alaska's daughter cured of blindness by cervical manipulation, and the lack of consideration in her husband who chose to be acromegalic without deviation of the spine. He died—and deserved to, or so I seemed to detect. Each case-history ended with the moral, monotonously drawn, "We must not jump at conclusions."

Chiropraxis now has a firm grip upon San Francisco, but it had not been without a struggle, for those villainous doctors (how thankful I was that I had not slipped so far as to reveal my profession) had done all they could in an endeavour to make it illegal. Eventually victory had been easy. Deft manipulation of the cervical spine had cured a boy who hitherto had squinted like an owl. It was only necessary to send him round the town to gaze each citizen straight in the eye, while at the same time displaying an early school photograph, for all prejudice to be overcome. The chiropractic law was passed.

I was thankful when we passed into cloud which disturbed our even flight. The flow of words gradually ceased, a hand moved surreptitiously to handbag and a *pill* was passed quickly into her mouth.

* * *

Overheard in out-patients (as chest physician wearing red goggles walks through to the X-ray department)—"Look, Mummy, that spaceman from Mars smiled at me."

Letters to the Editor

THE PLACE OF HUMAN BIOLOGY IN MEDICAL EDUCATION

SIR,—I read Dr. Tanner's article of June 7 with considerable interest. I have two objections, however, to his preclinical curriculum: it is too long and it is too vague. By the end of his second year the medical student should be ready to commence his clinical course and he should begin it with a sound knowledge of the development, structure, and normal functioning of the particular and peculiar creature on whom he is going to practise his skill as a doctor.

There is no sensible reason, although there are plenty of "academic" reasons, why he should not commence his anatomy, physiology, and biochemistry as soon as he enters the university. For all practical purposes he will have done enough chemistry and physics and general biology at school. Most of Dr. Tanner's curriculum could be included in a revised and reformed anatomy and physiology course extending over a two-year period, but however useful a knowledge of cellular biology, genetics, evolutionary theory, constitutional variability, and the use of statistical method may be, an accurate and complete knowledge of gross anatomy and of the basic functions of the body is essential. This does not mean that a great deal of detail could not be removed from the textbooks, but what is retained must be taught well and understood at the time it is being taught. I agree that further detail can most usefully be added later in relation to whatever specialty has been selected by the student, but this also applies to the whole content of the preclinical course.

A great deal of our present trouble is due to the tradition of teaching subjects such as anatomy, pathology, and biochemistry in water-tight compartments. Once these subjects are introduced into the curriculum they should remain in the curriculum and continue into postgraduate studies, but, as in other spheres, the method and timing of the introduction is very important. Once the essential framework of a logical and not over-ornate curriculum has been established there is a place for various subsidiary activities such as films, visiting lecturers, inter-departmental "brains trusts", &c., but these should not be looked upon as a means to make the fundamental process of learning the basic subjects more attractive. Grammar must come before rhetoric, and sound accurate knowledge must not be smothered in a foam of scientific enthusiasm.

The construction of a revised and up-to-date curriculum requires new textbooks written not in isolation but as units of a curricular library, and especially new teachers who take their responsibility as teachers as seriously as they take their research work or their clinical duties. The art of great teaching must be restored to its proper place. Teachers and textbooks can both be produced in time, providing a whole medical school is willing to attempt the experiment as a team, but there is little hope of much improvement by a process of uncorrelated departmental tinkering. We have been at that long enough.

Department of Anatomy,
The Queen's University of Belfast. JAMES H. SCOTT.

THE PREDICAMENT OF THE BLADDER

SIR,—The urinary bladder has a life of unparalleled hardship. In the male it is encumbered by the prostate; in the female it is buffeted by the fœtal head. Like many another mass-produced article, it is poorly finished—and substandard bladders with such obvious flaws as diverticula and ectopia vesicæ are still foisted on a long-suffering public.

The unfortunate organ is wantonly assaulted by the gynæcologist, the general surgeon, the urologist, the proctologist, the obstetrician, and the abortionist. Germs, tumours, and stones flourish within it, and its seclusion is rudely disturbed by bits of wire, knitting needles, and sundry other objects introduced by owners who are perverse, inquisitive, or just plain careless.

Its double function, to hold water and yet to pass water, makes a paradox which often confuses the young and inexperienced bladder—but even veteran bladders may fail in their duty through no fault of their own. To be incontinent, that is a misfortune which the bladder accepts with sardonic stoicism, only sorrowing at the misery which its defection may bring upon a kindly owner, upon a master who has treated it well. But retention: that is the culminating, and the cruellest, blow. Long and bitter experience has taught the bladder that this dread event is a herald of doom. It cries aloud in its agony and fear, and it will not be comforted. Neither faith nor potions will avail it now. The surgeon, and only the surgeon, can put an end to its torture.

Here, perhaps, is a dictum of our craft: "an obstructed tube is the only absolute indication for surgery". It matters not whether the tube is urethra or gullet, ureter or bowel, blood-vessel, windpipe, or bile-duct. We have no choice in this surgical variant of Hobson's Law.

It is curious that the bladder, in this moment of its greatest need, when it comes before the surgeon as a suppliant, should seek, so often, to deceive him. It is not above masquerading as an ovarian cyst, a pelvic abscess, or even a pregnant uterus. Two cases of this base ingratitude have recently come under my care.

The first was a man of twenty-seven who was admitted with pain in the perineum, high fever, and a bladder distended to the umbilicus. Small quantities of urine could be voided, with pain and difficulty, if he adopted the knee-elbow position. An X-ray showed a rounded opacity one and a quarter inches in diameter at the base of the bladder.

The patient was returned to the X-ray department with a request for oblique and confirmatory views of the "vesical calculus". No further radiographs were taken, but I was courteously reminded that the penis, photographed end-on, throws a circular shadow approximately one and a quarter inches in diameter!

The patient's retention was reflex, and his perineal pain was due to osteomyelitis of the sacrum. I subsequently drained half a pint of pus from behind his rectum and above the levator ani. The pus grew *Staphylococcus aureus*, and his convalescence was uneventful. He passed water normally from the seventh postoperative day.

The second patient was a sixty-year-old man who had passed no urine for forty-eight hours. His prostate was palpably enlarged and the distended bladder could be felt above it.

He was (and, curiously enough, still is) a Christian Scientist, and at first declined all aid. However, we felt that time was on our side, and a little later he allowed us to withdraw forty ounces of urine from his exasperated bladder. This was his only concession and he adamantly refused any operative interference.

For a week we eyed each other with mutual hostility. The catheter was removed on several occasions, but no urine escaped, the pain returned, the bladder was again palpable at the umbilicus. He then agreed to operation, provided that we would take a second opinion from Mr. X, his Christian Science practitioner. This we did, and a pretty bizarre opinion it was! Nevertheless, I feel bound to admit that Mr. X's views on the pathogenesis of this particular malady were no more absurd than my own.

When the patient was brought to the theatre, his bladder was still distended to the umbilicus, a phenomenon which we attributed to the withdrawal of his catheter some hours earlier—as a prophylactic against any last-minute repentance. A mid-line incision exposed a large swelling which was clearly not the urinary bladder. The peritoneum was opened, and the swelling proved to be an enormous cyst, filling the pelvis and squashing the unfortunate bladder into the left half of the abdomen. The cyst was removed without any great difficulty, and was shown to have originated in a presacral neurofibroma The bladder, relieved of its unwelcome neighbour, at once resumed its functions

I hope your readers will agree that there are several morals, as well as an extraordinary number of mixed metaphors, in this narrative

Barnet General Hospital,
Barnet.

V J. DOWNIE

INTESTINAL ANGINA

SIR,—I was very interested in your leading article of June 7 I must, however, take exception to your statement in the first paragraph—" and they must not be confused with the common abdominal radiation of cardiac anginal pain "

Cardiac anginal pain very rarely radiates to the abdomen. Typically this is retrosternal and may radiate to either chest, shoulder, or arm Less frequently it radiates to the jaw, and through to the back I have paid particular attention to this radiation during the last five years In only one case, proved at postmortem to have a cardiac infarct, did the pain radiate to the abdomen, even in this case there was a possible alternative explanation

This is a very important feature of cardiac anginal pain If it is accepted that this rarely radiates below the xiphisternum it becomes an extremely important differential diagnostic point

Chichester

JOHN D -WHITESIDE

SIR,—In reference to your editorial on " intestinal angina ", I should like to remark that what has been described recently by Mikkelsen under this term is the syndrome described many years ago by Professor Ortner and by myself and to which I gave the name of " intestinal angiospastic syndrome " A new name does not mean a new disease, particularly when that name will cause great confusion in clinical work

As I pointed out in my description,[1] the intestinal angiospastic syndrome occurs in individuals somewhat advanced in age and frequently after a prodromic period of vague abdominal disturbance It consists in sudden attacks of acute diffuse abdominal pain reaching its maximum in about one minute, lasting some ten or fifteen minutes and accompanied in its last phase by tympanism and sometimes by pallor, acceleration of pulse, and even collapse These attacks occur after meals when the digestive tube has been loaded with food, principally with foodstuffs producing gas through fermentation, and in some cases following exertion, mainly after meals It has to be distinctly differentiated clinically from cases of angina pectoris with epigastric pain and it is for this reason that the terms intestinal or abdominal angina are confusing I described the intestinal angiospastic syndrome as one of the syndromes manifesting atherosclerosis of the intestinal arteries, the other being acute mesenteric thrombosis which, in some cases, follows the attack of this angiospastic syndrome

Enlarging on the study of Ortner I pointed out the coincidence, in both these syndromes, of manifestations of angina pectoris and of atherosclerotic obliterans arteriopathy of the limbs, such manifestations in some cases following each other in time, as in a case described in collaboration with Dr Catsaras in this journal [2]

The work of the American authors you quote is important in directing our attention again to intestinal atherosclerosis and particularly in indicating the possibility of surgical treatment It is, however, necessary to stress the significance of the original clinical descriptions and to maintain the original terms through which the confusion with angina pectoris with epigastric pain is avoided Precision in terms is essential in clinical medicine

London, W 1

A P CAWADIAS

ADRENALINE CREAM

SIR,—I was surprised to read that Dr Hume Kendall and his associates (May 17) had expended so much effort in proving that adrenaline cream is ineffective in the treatment of degenerative arthritis of the spine I have never suggested, as Dr Kendall seems to believe, that the cream relieves the rheumatic syndrome by producing hyperæmia or analgesia when applied locally I have consistently stressed that adrenaline cream works *only* if it is applied to the myalgic or " trigger " spots of muscles in a state of spasm, when it relieves the pain of " fibrositis " and other forms of soft-tissue rheumatism

Since Good [1] first drew attention to them, the existence of trigger spots and their capacity to cause pain and disabilities commonly designated as " rheumatic " have been confirmed by several independent workers, notably by Bonico [2] Yet in those extensive trials of the cream which have given negative results, the treatment has never been applied to the myalgic spots [3]

Surely it is essential for the evaluation of any therapy that trials should be carried out in the manner indicated in the primary research As yet—after a decade—this has not been done, except by Howell,[4] who obtained a positive result

May I suggest to Dr Kendall and to others interested in the treatment of the chronic rheumatic diseases that if further trials are contemplated, the technique of treatment should be the one I have described [5]

London, W 1

LOUIS MOSS

COLOURED TABLETS

SIR,—The practice of colouring and coating pharmaceutical tablets has grown considerably during recent years, especially among companies which have begun to operate in Britain from overseas The *British Pharmacopœia* has hitherto resisted the inclusion of colour and coating except for good pharmaceutical reasons, such as protection against deterioration or the masking of unsightly colours in the natural material

The manufacturers claim that the improved elegance achieved justifies the new practice, and they also claim that it is necessary to enable the industry to compete in foreign markets So strong has this pressure become that the *Pharmacopœia* has now had to take the course of admitting the manufacturer's tablet, coating, colouring, and all, or not have it in the *Pharmacopœia* at all [6]

Some of us believe that the colouring and coating of tablets and capsules, except for the reasons formerly accepted, increases the danger of poisoning among children, though proof of such an assertion is difficult to obtain

A preliminary experiment was recently carried out in the Westminster Children's Hospital along the following lines

'Smarties', a brand of coloured sweets favoured by most children, were segregated into their constituent colours and offered, along with some specially prepared white ones, to children attending the clinics The dishes contained equal numbers of tablets and were randomly arranged on the tray The number of each taken during the experimental period was

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[1] Cawadias A P Diseases of the Intestines pp 229-232 London 1927 *C R Soc Biol Paris* 1922, 74, 591

[2] Cawadias, A P, Catsaras, J *Lancet* 1923, i, 949

[1] Good M. *Lancet*, 1940, ii 237

[2] Bonico J J *J Amer med Ass* 1957, 164, 732.

[3] Moss L. *Med Wld* 1951, 75 285

[4] Howell, T H. *Lancet*, 1950, ii 305

[5] Moss, L. Rheumatism and You. London, 1955

[6] See *Lancet* April 5, 1958, p 726

Red	209	Orange	185	Brown	152
Black	145	Pink	132	White	132
Green	114	Mauve	111	Yellow	106

If white is regarded as a colour, the only marked preference is for red and orange

In a second experiment, a dish of mixed smarties—the normal assortment—was offered alongside white ones In this case the preference for the coloured tablets was of the order 2 1

It is true that the smarties are known and appreciated by the children and this gives a bias against an unknown white commodity, but it does seem reasonable to conclude that the more one makes medicinal tablets look like smarties, the more likelihood there is of children taking them

Experiments of different design are being prepared to remove some of the bias this preliminary experiment obviously has, and these we hope to publish in due course

Westminster Hospital,
London, S W 1

HERBERT S GRAINGER

_ We publish on p 1308 a paper by Dr Jolly and Dr Forrest describing the results of an experiment with coloured tablets —ED L

STRUCTURAL DETAILS IN MYCOBACTERIA AFTER HYDROLYSIS

SIR,—The presence of soluble material (cytoplasm and external lipid layer) in the cells of mycobacteria has been held responsible for the difficulty in discerning morphological details within the cell [1] A method is here reported by which an insoluble specifically inert material containing undamaged cell walls and electron-opaque granules, was isolated from *Mycobacterium tuberculosis* after removal of the unstructured soluble cellular material

An eight-week-old culture of *Myco tuberculosis* H_{37} R_V grown in glycerin-broth, was heated for 30 min at 120°C and then harvested in 10 volumes (w/v) of *N*KOH solution and incubated for 2 hr on a boiling water bath under a reflux condenser The homogeneous highly turbid suspension that resulted after heating was washed with *N*KOH solution in the centrifuge (15,000 *g*) and the white residue allowed to digest with trypsin for 12 days at 37°C under toluol [2] The remaining insoluble material was washed with distilled water by centrifuging at 18,000 *G* and extracted with 50 volumes (*w*/*v*) of formamide for 6 hr at 100°C The stable suspension was separated in the centrifuge (20,000 *g*), washed and resuspended in distilled water The insoluble fraction obtained in this manner contained 10 5% nitrogen, 7% carbohydrates, and 17 9% ashes It represented 0 3% (dry weight) of the original bacillary material and was specifically inert when tested in vitro or in the animal (work to be published)

Examinations of the insoluble fraction showed, as revealed in the light microscope after staining,[*] non-acid-fast, transparent bacillary bodies which stained faintly pink with Ehrlich's dye and contained one or several metachromatic dark violet granules (fig 1*a*) By comparing the electron-micrograph of the insoluble fraction (fig 1*b*) with the images previously obtained by direct or ultra-thin section examinations of mycobacteria[3, 4], it may be seen that the treatment resulted in a strikingly increased permeability of the bacterial body to the electron beam The cells appeared like "flat collapsed sacs" which obviously represented the bacterial cell walls, and contained well-defined opaque granules resembling in shape and disposition the metachromatic granules viewed in the light microscope The alkali-trypsin-formamide-resistant granules, staining metachromatically and electron-opaque, can obviously be identified with the "volutin-metaphosphate" granules recently studied by Glauert and Brieger [5]

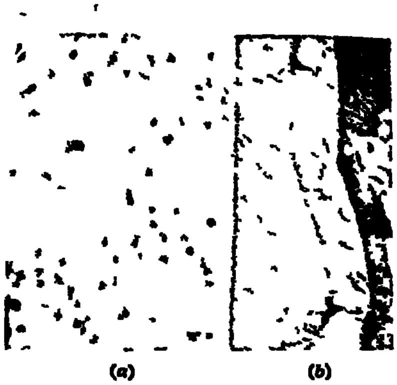

Fig 1—Insoluble fraction (*a*) photomicrograph (×2500), (*b*) gold-shadowed electron micrograph (×15,000)

A significant result concerning the intimate structure of these granules was noted when the insoluble fraction was subjected to a suitable treatment for 6 hours at 65°C with 0 5 *M* trichlorate acid and examined by the light and electron microscopes Fig 2[†] indicates that the metachromatic granules were thoroughly dissolved out in trichloracetic acid, while under the electron microscope there was no detectable change under these circumstances "Volutin" granules of mycobacteria are, therefore, not homogeneous, they contain at least two chemically separable constituents carrying respectively the metachromatic and electron-opaque characters

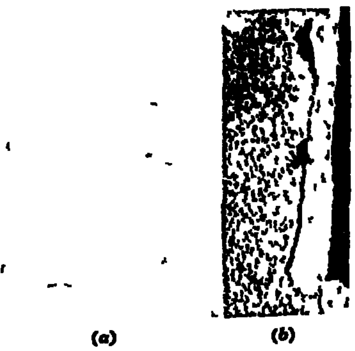

Fig 2—The insoluble fraction after trichloracetic-acid treatment (*a*) photomicrograph (×2500), (*b*) gold shadowed electronmicrograph (×8500)

Cantacuzino Institute,
Bucharest, Rumania

G G GANCEVICI

UNEXPLAINED FACIAL SPASM

SIR,—Recently I was confronted with a curious case of facial spasm

A girl of 10 was referred to the Birkenhead Children's Hospital with a spasm consisting of depression of the mandible and retraction of the tongue, beginning an hour after extraction of two left lower molars two days before Deglutition was possible, but not mastication There was no other spasm, and no history of recent injury Dislocation of the jaw was excluded

On examination, the child could not move the jaw or tongue Chvostek's sign was positive on both sides in the distribution of the mandibular division of the 5th nerve Trousseau's sign was negative, and there was no carpopedal spasm Serum-calcium was 10 2 mg per 100 ml

The condition gradually abated over the next three days, after which the child could eat normally Chvostek's sign persisted for five days

It was suggested that the increased nervous irritability may have been due to facilitation at the synapses of the reflex arc, involving the trigeminal and facial nerves, and brought about by the persistent stimulation of the former nerve

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[1] Knaysi, G *Ann Rev Microbiol* 1956, 74, 12

[2] Pillemer, L , Blum, L , Lepow, I H , Wurz, L , Todd, E W *J exp med* 1956, 103, 1

[3] Mudd, S , Takeya, K , Henderson, N J *J Bact* 1956, 72, 767

[4] Toda, T , Koike, M , Hisaki, N , Takeya, K *ibid* 1957, 73, 442

[*] Selective staining for both cell walls and granules was performed as follows smears were fixed for 2 min in 1% osmic acid, washed in running water and treated for 5 min with an aqueous freshly prepared solution containing 15% tannic acid and 10% K alum After rinsing in distilled water, Ehrlich's aniline crystal violet was poured onto the slide and incubated for 10 min at 37°C The stained smear was passed to water again, then Lugol's iodine solution was added (3 min), it was finally rinsed in distilled water

[5] Glauert A , Brieger, E *J gen Microbiol* 1955, 13, 310

[†] Kindly made by Dr A Petrovici and Ing R Davidescu

Any other explanation of this unusual sign would be welcome

Ormskirk County Hospital,
Ormskirk, Lancs

WARREN DURRANT

ESSENTIAL FATTY ACIDS, LIPID METABOLISM, AND ATHEROSCLEROSIS

SIR,—Our interest was aroused by the article by Dr Kinsell and his colleagues (Feb 15)

Though we are not convinced of the cholesterol-depressing action of essential fatty acids in relation to atherosclerosis, our own observations confirm some of the propositions of Dr. Kinsell and his colleagues There is some evidence[1] of the direct conversion of linoleic to arachidonic acid we therefore used soybean oil, one of the richest sources of linoleic acid Meanwhile it appears[2] that the favourable cholesterol-depressing effect is limited to linoleic and arachidonic acids

10 patients (8 men and 2 women) with hypercholesterolæmia were investigated In 8, signs of coronary sclerosis were found (myocardial infarction, angina pectoris) 2 had hypercholesterolæmia without any clinical symptoms of vascular lesions In 3 patients the disease was complicated by diabetes, in 1 by hypertension The average age of the patients was 55·5 years

The first week after admission was a control period and the patients received a diet similar to the one they were accustomed to Blood samples were taken twice during this period

6 patients (group *a*) then received a diet providing 30 calories per kg of ideal body-weight, fat yielding 30% of the calories, protein 18%, carbohydrate the remainder All free fat was supplied as soya oil The vitamin-C intake was about 100 mg a day 4 patients (group *b*) received a diet isocaloric with that of the control period, but all free fat was supplied in the form of soya oil The average oil intake was 41 5 g a day

9 patients had this treatment for five weeks, and 1 for eleven weeks, and 1, as an outpatient, for ten weeks

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[1] Mead, J F, Howton, D R *J biol Chem* 1957, 229, 575
[2] Hegsted D M, Gotsis A, Stare, F J *J Nutr* 1957, 63 377

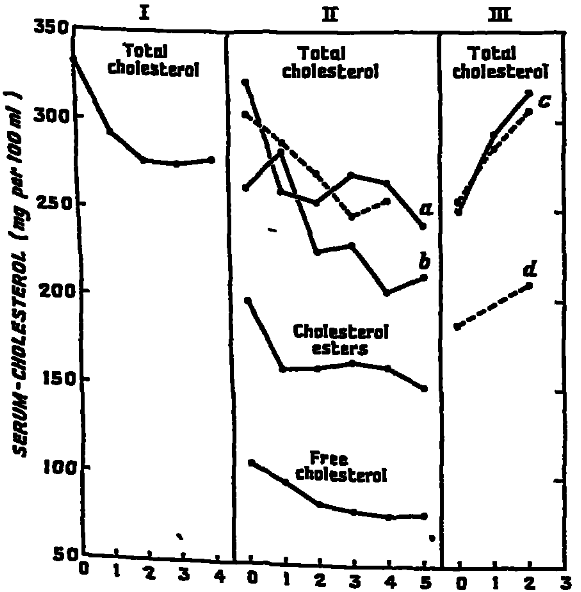

Fig 1—Serum-cholesterol levels before (I) during (II) and after (III) the period of soybean oil diet Broken line Findings in patient taking olive oil *a b, c, d* see text

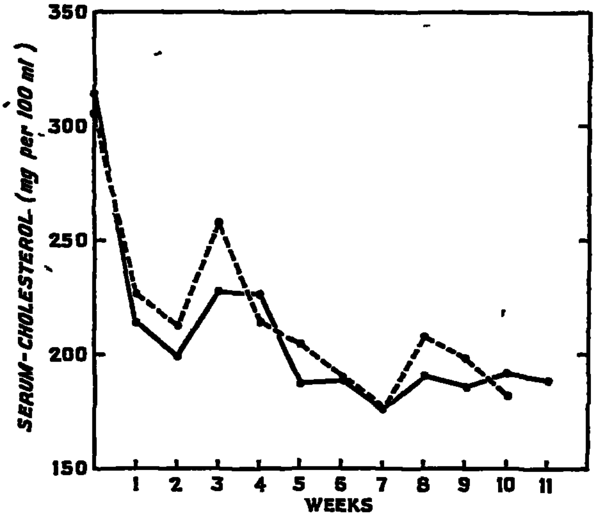

Fig 2—Serum-cholesterol changes in outpatient (broken line) and hospital patient (continuous line)

4 patients with hypercholesterolæmia who were admitted to hospital but did not receive the soya oil served as controls In another patient the soya oil was replaced by olive oil

The serum-cholesterol in the control patients reached a somewhat lower level than the initial values In the group receiving the soya oil (fig 1) an obvious fall in the serum-cholesterol level was noted, which persisted throughout treatment There was no substantial difference between groups *a* and *b* 2 patients were followed after the dietotherapy had been stopped and a rise of the serum-cholesterol was noted, though in one patient (*d*) the caloric value and fat content of the diet remained unchanged and in the second patient (*c*) the caloric value of the diet was even reduced from 2700 to 1800 calories, and the fat content from 95 to 65 g, but the soya oil was replaced by animal fats

All our patients receiving the soybean oil felt better, though the blood-coagulation and the lipoprotein pattern remained unchanged. A shift of the lipoprotein fractions from beta to delta was insignificant We think that the analogous results obtained in an outpatient exclude the possible effect of bed rest and other non-dietary factors on the cholesterol level (fig 2)

Institute of Human Nutrition,
Prague, Czechoslovakia

J VAVŘÍKOVÁ

PREMEDICATION FOR OUTPATIENT ELECTROCONVULSION THERAPY

SIR,—Electroconvulsion therapy (E C T) for specific mental illnesses is being increasingly used with success in outpatient departments, not only in order to save patients admission to hospital but also to allow them to continue their work whilst receiving such treatment Further, if given in a general hospital it is acceptable to people who, although in urgent need of it, could not accept what they regard as the “ stigma ” of attending or entering a mental hospital

In spite of these advantages, however, there remains the very real problem of the apprehension and anxiety which precedes E C T even when modified with thiopentone and suxamethonium chloride, as is our practice It was to deal with this problem that a small clinical trial was carried out, and, although no control group has yet been studied, the results achieved were of great practical value

30 patients, all attending for outpatient E C T at a general hospital and all complaining of such pretreatment anxiety

and apprehension (all having had one or more modified E C T s) were given a small supply of methylpentynol carbamate ('Oblivon C'), with instructions that on the morning of treatment, two 'Ovets' (200 mg) should be taken on rising and two more about an hour before attending hospital—i e, about 1 30 P M

There was a striking improvement in the attitude of most of these patients Grading of their reactions was rated as "much improved", "improved", "no change", or "worse" 20 patients claimed to be "much improved", 8 more were "improved", only 2 patients felt no different, and none felt worse

I am aware of the failings of such a trial, both from the smallness of its numbers and the absence of a control group These will take time to rectify, although it is hoped to do so

The importance of these apparently excellent results lies not only in the relief of the pretreatment fears but also in the fact that patients urgently requiring such treatment now feel able to accept it, whereas previously their very real fear and terror prevented them from doing so Hence this letter

Hellingly Hospital,
Hailsham, Sussex
J F COLLARD

WORLD HEALTH ASSEMBLY

SIR,—In your note of June 7 on the tenth annual commemoration session of the World Health Organisation, you report that Dr Brock Chisholm, lately director-general of W H O, said that the Organisation had come to be widely recognised for efficiency This was, he thought, due to the unique character of the Executive Board, whose eighteen members act purely as health experts and not as representatives of governments "Any attempt to convert the Executive Board into a political body would threaten the future of the Organisation"

Some considerable experience in the conduct of small voluntary associations leads me to believe that those responsible for such associations are likely to achieve efficiency similar to that of W H O, on its more important level, whenever they adopt the expedient of accepting guidance from advisors not primarily concerned with authority

Braziers Park,
Ipsden, Oxon
J NORMAN GLAISTER

A USEFUL ACCESSORY SUTURE

SIR,—I think it might interest people to know about a little procedure or "dodge" I have used for many years to facilitate the removal of sutures It is particularly useful in children, and has come through many years' trial very satisfactorily

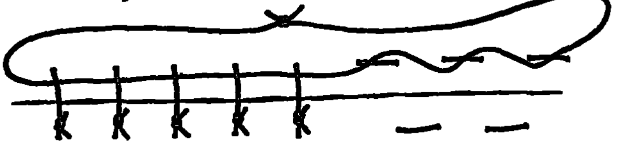

Fig 1—Continuous thread in position

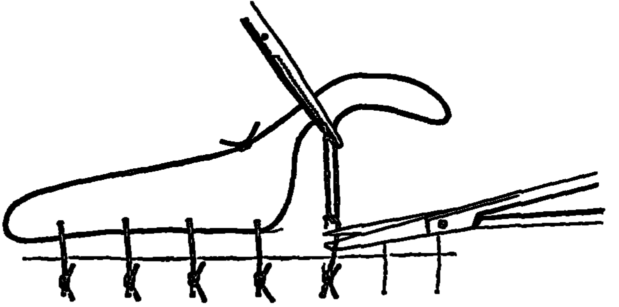

Fig 2—Removal of sutures

A continuous thread of a material different in texture and colour from that used for the skin suture is passed under each skin suture The thread therefore runs parallel with the incision and lies quite loosely in between each two sutures (fig 1) Removal is facilitated (fig 2), the effect of the œdema round the sutures is completely offset, and, even in a poor light, sutures may be removed quickly and painlessly even in a very young or very nervous patient

Liverpool, 1
BRYAN MCFARLAND

PROTHROMBIN ESTIMATION BY THE TWO-STAGE METHOD

SIR,—Dr Wright and his colleagues (May 31, p 1157) report evidence of slow coagulation when heparinised blood circulates through an extracorporeal bypass Fibrinogen concentration, antihæmophilic activity, and the platelet-count all fell to about half their normal values However, the prothrombin, estimated by the two-stage area method of Biggs and Douglas,[1] showed a striking initial increase

It may not be sufficiently realised that results obtained by this method are directly comparable only if the fibrinogen concentration and the activity of progressive antithrombin are each identical in the plasma samples tested, Where they differ, corrections must be applied to the results (as area-units observed) before the comparisons are made

Fibrinogen concentration—It is well known that when blood clots, some thrombin is removed by fibrin Hardisty and Pinniger[2] added varying quantities of purified fibrinogen to the plasma of an afibrinogenæmic girl, and found that about half the thrombin liberated was bound by the normal range of fibrinogen concentration and would thus remain undetected in tests on normal plasma Their data show the thrombin area observed to be linearly related to the square-root of the fibrinogen concentration (*w/v*), the observed area fell by 2 2 thrombin mins per root mg % increase in the fibrinogen concentration in the reaction

From the theoretical model discussed below, it may be anticipated that the slope of this regression would vary inversely with antithrombin potency, and it is possible that deficiency or excess of prothrombin might also affect the relationship, and thus further complicate the interpretation of the test Without further investigation, it does not seem possible to calculate the appropriate corrections

Progressive antithrombin—Biggs and Douglas[1] based their area method on the close correspondence between observed two stage curves and a theoretical model derived from consecutive first-order reactions, they were careful to point out the implication that the area under the curve will not provide a measure of prothrombin "unless the level of antithrombin is normal"

Imagine an effectively first-order system containing a *finite* quantity of prothrombin (measured in equivalent thrombin units), a, with thromboplastin and antithrombin, supposedly in excess and therefore constant, denoted by P and A respectively *Then the* concentration of thrombin, y, at time t is given by

$$y = \frac{aK_1}{K_2 - K_1}\,(e^{-K_1 t} - e^{-K_2 t})$$

where $K_1 = k_1P$ and $K_2 = k_2A$, k_1 and k_2 being the reaction constants The area under the curve relating thrombin concentration to time is a/K_2, and is thus inversely proportional to A The relevant measure of antithrombin is not, of course, the total quantity of thrombin which can be destroyed by the plasma in unlimited time,[3] but the rate at which thrombin decays

Therefore, to correct for differences between A_C and A_T (the antithrombin in the control and test plasmas respectively), multiply the test area by K_T/K_C, the observed rates of decay of thrombin added to test and control citrated plasma respectively,[4] which are estimates of K_2 for the two plasmas The decay is exponential, so that log thrombin concentration is *linearly related* to sampling time, and the slope of this line (the fall in log thrombin units per unit time, say K log units per min) is the required measure of antithrombin activity

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1 Biggs, R., Douglas, A S *J clin Path* 1953, 6, 15
2 Hardisty, R. M, Pinniger, J L *Brit J Hæmat* 1956, 2, 139
3 Astrup, T, Darling, S *Acta physiol scand* 1942, 4, 293
4 Quick, A J The Physiology and Pathology of Hæmostasis, pp 164-165 London, 1951

The position is a little complicated by Seegers'[5] finding that part of the antithrombin activity (antithrombin IV) can be demonstrated only during the conversion of prothrombin to thrombin, and so could remain undetected by this procedure However, we have been able to compare the rates of decay of thrombin added to citrated plasma with and without the concomitant addition of brain extract and calcium chloride, and have not found significant differences. We believe that antithrombin IV may be ignored in determining the two-stage correction

In slowly clotting plasma we have found little change in serial estimates of K The second correction is therefore probably unimportant in the bypass experiments, but the fibrinogen effect should obviously be allowed for since the fibrinogen concentration fell markedly during the period of observation

Dr Wright and others confirmed their anomalous prothrombin results by the acid-precipitated-globulin method[6] Unfortunately, we have found that the "globulin" precipitate also contains fibrinogen (in one experiment, about a quarter of that in the original plasma), so that variations in plasma-fibrinogen concentration may well be reflected in the fibrinogen content of the solution prepared from the precipitate

We therefore feel that the observed increase in prothrombin during slow coagulation is probably more apparent than real, and we would be interested to learn whether the authors feel that it is explicable on the lines we have suggested Of course, we fully accept the main conclusion that slow coagulation was occurring in the bypass

Louis Jenner Laboratory,
St. Thomas's Hospital and Medical School,
London, S E.1
G I C INGRAM

Medical Research Council's Statistical
Research Unit,
London School of Hygiene and Tropical Medicine,
London, W C.1
P ARMITAGE

PHYSICAL CHANGES IN THE PROLAPSED DISC

SIR,—I should like to comment briefly on your annotation of June 7

Attrition of the annulus is only one of the results of decreased imbibition pressure in the nucleus, and possibly not the most important one, as hydrostatic effects most certainly occur as well. It seems to me, on the basis of the work to which you refer, unnecessary to postulate a hyperhydration of the nucleus, particularly as this has never in any case to my knowledge been satisfactorily demonstrated, and as the inefficiently functioning nuclear gel will itself produce precisely these effects because it reacts to increased pressure by liberating an abnormally large quantity of fluid It is thus, I think, which is responsible for successive ruptures of the already weakened annulus, and clinically for the acute attacks of pain which are common on the patient's first moving after a period of rest.

The difference between the deterioration of the prolapsed disc and that of the physiological ageing disc is, as you imply in your annotation, a matter for further investigation. I have suggested that the orderly replacement of polysaccharide by collagen in the course of normal ageing could be the factor that prevents hydrostatic effects in the elderly Investigations now being undertaken here by Dr Peter Mitchell suggest that that will in fact prove to be the case Significant changes have also come to light in the content and possibly the composition of the polysaccharide, which we hope to report in due course Indeed, so many variables exist that I cannot share your difficulty in understanding why nuclear desiccation in the elderly should differ from that in the deranged disc. At the risk of perpetrating the inaccuracy that is inherent in all generalisations, one might perhaps say that the difference between normal and pathological ageing is that only the latter will prove to be pathological.

Royal Infirmary,
Aberdeen.
NEIL G C HENDRY

SIR,—In your annotation you quote Hendry's work on the hydration of the prolapsed disc, and go on to say "If desiccation in discs is a major factor in their prolapse, it is difficult to understand why the elderly remain relatively free from major disc derangement" In the article you quote, you will find a plausible explanation

Stresses through the vertebral body are balanced partly by imbibition pressure of the nucleus—the power to retain water which enables cacti to live in the desert and mushrooms to lift paving-stones—and partly by the annulus fibrosus The nucleus consists of a lattice-work of collagen in which is embedded a mucoprotein gel which retains fluid by imbibition pressure In the ageing nucleus the proportion of collagen increases and gel decreases

As the imbibition pressure is reduced, the annulus bears a greater strain, and the character of this strain changes from alternating pressure and tension to a continuous force which may rupture the annulus and allow prolapse of the contained nucleus

As ageing continues, the proportion of collagen rises further Eventually the nucleus is completely fibrosed, and prolapse is virtually impossible

Institute of Orthopædics,
London, W 1
I G MACKENZIE

DEATH OF A BOXER

SIR,—Those of us who were at school nearly half a century ago were told that a sense of proportion was a good thing to acquire and keep

People have been struck on the head by cricket balls and died therefrom One of these, if memory serves, was a Royal Prince. No more cricket?

Necks have been broken playing rugger I had one such in my practice and the patient died. No more rugger?

A tough doctor friend who won the inter-Hospitals boxing at both middle and heavy weight in the same competition played rugger for his university and cricket and tennis for his county, and for many years rode to hounds as if the devil was after him, came to no harm till, in riper years, he took to golf Leaning over to scoop his ball out of a deep bunker he slipped and fell, dislocating his shoulder Clearly, then, no more golf

Meanwhile, of course, let there be no more mountaineering, steeplechasing, or polar exploration all too risky

Most of us, I suppose, die in bed Perhaps we should sit up all night Really, Sir, do we want, or expect, to live for ever?

Crediton, Devon.
L N JACKSON

SIR,—I find it difficult to appreciate the viewpoints of those who maintain that bashing the skull is good for it and those who have to carry out experiments on animals to show that injury to the skull is bad for it Surely the whole design of the skull is such that the structures within it are protected against the normal injuries likely to be encountered in the ordinary rough and tumble of life, but that is no excuse for submitting it to deliberate trauma in the interest of sport

If the general public cannot adopt a common-sense attitude towards boxing and demand its abolition, I suggest that they be asked to treat their skulls with the same respect that they treat their television sets No-one in their right senses would deliberately hit a television set or box its aerials, yet, schoolmasters and parents continue to box children's ears and boxing is still taught as a means of self-defence, although wrestling is safer and more efficient Moreover, as long as boxing is taught in schools and boys' clubs, professional boxing will continue to thrive

At a recent debate on this subject held among patients at the Lancaster Moor Hospital I discussed the subject in this manner and the voting went in favour of boxing being abolished by a small majority One can only hope that they represented a cross-section of the general population

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[5] Seegers W H., Johnson J F Fell C. *Amer J Physiol* 1954, 176, 97
[6] Douglas, A S, Biggs, R. *Glasg med J* 1953, 34, 329

Lancaster Moor Hospital R PAKENHAM-WALSH

TIME AND THE NERVOUS SYSTEM

SIR,—Thank you for publishing Professor Woodger's definition of an A-line (June 7) I find it difficult to understand why Dr Gooddy (May 31) should think it necessary to explain the well known—such as how a clock works or that joints are of two types (ball-and-socket or hinged)—and unnecessary to explain a difficult concept taken from a discipline different from medicine

He makes some propositions that I am not clear about, such as "There is no system of knowledge about time, to compare with the advanced systems of biology, physics, and chemistry" I wonder is the concept of time comparable with the positive sciences (by which I mean systematised collections of facts) he mentions? Would the assertion "There is no system of knowledge about length or depth to compare with the advanced systems of biology, physics, and chemistry" have any point?

Not everyone would agree with his allegation that the interstate between neurology and psychiatry is neglected, nor that neurology lies at the junctional point of philosophy and science—is there such a junctional point? I cannot see how the neurologist, who may have no training or experience in psychology, psychiatry, semantics, logic, and philosophy can be claimed to be in the best position for the investigation of disorders of the time sense Let me hasten to state I know several neurologists who seem to me to have a knowledge of these disciplines but as far as I can see they acquired it in spite of their training in neurology

It may be that rhythmic activity of the nervous system is related to time appreciation The electroencephalograph demonstrates such rhythmic activity but surely it does not prove any connection with time appreciation On the contrary, alpha rhythm "which shows final abstraction from all other rhythms" disappears with visual activity but time appreciation continues

Shenley Hospital,
near St Albans RUSSELL BARTON

THE CERVICAL AORTIC KNUCKLE

SIR,—In April, 1953, two of us reported[1] the case of a young man whom we had observed periodically since we first saw him, at five years of age, with a pulsating swelling in the right side of his neck, extending as high as the hyoid bone Exploration at that time suggested that it was the arch of the aorta following a second exposure a few months later the overlying deep cervical fascia was reinforced with fascia lata taken from the patient

In 1953 it was noted that, since the operations thirteen years before, there had been no great change in the cervical aortic knuckle, which bothered him slightly if at all he had been regular in attendance at his work as a storekeeper and had had no serious illnesses In March, 1957, he was readmitted complaining of some difficulty in swallowing certain foods, such as potatoes and meat The dysphagia had been present for about six months and was increasing A vascular ring compressing the œsophagus was suspected and the evidence obtained by angiography supported this

On April 2, 1957, left posterolateral thoracotomy through the bed of the fifth rib (H R S H) confirmed the diagnosis The transverse retro-œsophageal segment of the aorta, the ligamentum arteriosum, and the right and left pulmonary arteries formed a vascular ring which fitted tightly around the trachea and œsophagus, the posterior wall of which was indented by it The ligamentum arteriosum was tense, nearly an inch in length, and formed the left part of the ring extending from the left subclavian artery at its junction with the aorta to the left pulmonary artery at its junction with the right branch After division of the ligament the constriction of the trachea and œsophagus was relieved and his dysphagia alleviated He remains well and free from symptoms a year later

In our first report of this case we drew attention to the condition of cervical aortic knuckle in a child Recognition of its nature is important since it has been mistaken for an aneurysm and operated upon with fatal result. We have presented this further note because, in cases of abnormality of the aortic arch, *it would seem reasonable to* suspect the presence of an intrathoracic vascular ring which, by encircling the trachea and œsophagus, may in the course of time cause dysphagia

A detailed discussion on the embryology of these cases will appear in an article by one of us (H R S H) shortly to be published in the *British Journal of Surgery*

Surgical Unit,
Welsh National School of Medicine,
Royal Infirmary, Cardiff

CECIL LEWIS
H R S HARLEY
LAMBERT C ROGERS

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[1] Lewis, C, Rogers, L *Lancet*, 1953, i, 825

Parliament

Proposed Amendment of Registration Procedure

ON June 11, under the ten-minute rule, Mr JOHN HYND, a former member of the General Medical Council, asked and obtained leave to introduce a Bill to amend the Medical Act of 1956 The wording of that Act, Mr Hynd said, had proved anomalous and the procedure it laid down cumbersome The amendments proposed in his Bill would affect two groups of doctors those who had qualified in this country before Jan 1, 1953, but who for some reason had not applied for registration, and those who qualified in this country because they held foreign or Commonwealth diplomas not recognised for registration Both these groups, irrespective of their previous experience, had still to do twelve months' internship in a hospital before they could obtain full registration His Bill would put these groups on the same footing as doctors with Irish or recognised foreign qualifications who could obtain full registration if they offered evidence of appropriate hospital experience

Mr Hynd's Bill would also simplify the administrative procedure for admitting doctors to the provisional register At present they had to produce a certificate of selection for employment and their qualifications had to be checked by the hospital and counterchecked by the board This often meant considerable delay, and as a result doctors might be practising for days or weeks in hospitals quite illegally before they had been formally admitted to the Provisional Register He suggested that we should return to the earlier procedure which left authority in the hands of the G M C

Mr Hynd assured the House that these changes had been discussed with the G M C, the British Medical Association, and other bodies who had all agreed that they were not only necessary but desirable

Princess Louise (Kensington) Hospital for Children

In the House of Lords on June 16, Lord STRATHCLYDE, replying for the Government to a question about the future of this hospital,[1] said that the Minister of Health had decided to approve the temporary use of two wards for maternity patients during adaptation of the maternity unit at St Mary's Hospital He could not approve the long-term use of the hospital for adults, but would review its future again towards the end of the period of temporary use, which would be about two years after adaptation had been completed

QUESTION TIME

A New Regional Hospital Board

Mr JOHN EDEN asked the Minister of Health if he had yet come to a decision as to the date on which it would be possible to set up a separate Wessex Regional Hospital Board for the

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[1] See *Lancet*, 1957, ii, 41

South West Metropolitan Region —Mr DEREK WALKER-SMITH replied I have decided that it will be possible to do so on April 1 next and I am taking the necessary steps to bring the new region and regional hospital board into being on that date

Morphine and Heroin Addiction Committee, 1926 (Review)

The Minister of Health, in consultation with the Secretary of State for the Home Department and the Secretary of State for Scotland, has appointed a committee with the following terms of reference

To review in the light of more recent developments the advice given by the Departmental Committee on Morphine and Heroin Addiction in 1926, to consider whether any revised advice should also cover other drugs liable to produce addiction or to be habit-forming, to consider whether there is a medical need to provide special, including institutional, treatment outside the resources already available, for persons addicted to drugs, and to make recommendations, including proposals for any administrative measures that seem expedient

The membership of the committee is as follows

Sir Russell Brain, F R C P (chairman), Laurence Abel, F R C S, D M Dunlop, F R C P, Donald W Hudson, M P S, A D Macdonald, M D, A H Macklin, M D, S Noy Scott, M R C S, and M A Partridge, D M

Emergency Telephone Lines for Hospitals

Mr HERBERT MORRISON asked the Minister whether he had considered the report on emergency telephone and other arrangements at Lewisham Hospital in connection with the Southern Region railway disaster at St Johns, and what action was being taken —Mr WALKER-SMITH In general the arrangements appear to have worked well, and I should like to take this opportunity of paying a tribute to all who took part in meeting a very difficult situation Detailed points have been discussed by representatives of the services concerned, and steps have been taken in this region to arrange for ex-directory lines at major hospitals and for a review of their telephone communications The report has been circulated to all regional hospital boards, and consideration is being given to certain matters by my officers with a view to further action if required

Hospitals Staffing Working Party

Mr KENNETH ROBINSON asked the Minister the terms of reference of the working party set up to consider the medical staffing structure of the hospitals —Mr WALKER-SMITH replied To study, in the light of experience of the hospital service since 1948 and of all other relevant considerations, the principles on which the medical staffing structure in the hospital service should be organised Mr ROBINSON What member of the Working Party is qualified to assess the special needs of the mental hospitals in relation to medical staffing, and whether, in view of the composition of the working party, it is the Minister's intention to exclude from their consideration the problem of mental hospital staffing —Mr WALKER-SMITH As the terms of reference indicate, the working party is to study the principles on which the medical staffing structure should be organised and not the number of staff required by individual hospitals The working party is well equipped to cover the hospital service generally and I see no reason to modify its terms of reference

Private Beds in London Hospitals

Mr HENRY HYND asked the Minister of Health how many private beds were now available in London hospitals, as compared with the number before the creation of the National Health Service —Mr WALKER-SMITH replied At Dec 31, 1957, 2255 beds were available under sections 4 and 5 of the National Health Service Act, 1946, in the Metropolitan Police District I understand that there were 2288 beds classed as private beds in the same hospitals shortly before the inception of the National Health Service, but as there was then no accepted definition of the term " private ", the figures are not strictly comparable.

Poliomyelitis Vaccine

In answer to a question Mr WALKER-SMITH said that by April 30 over 3 million persons in Great Britain had been vaccinated with two injections, just over $2^{1}/_{2}$ million were awaiting vaccination, and a further 500,000 were awaiting their second injection On that date the local health authorities held 1 million doses of vaccine and they had since received over 5 million more This was more than sufficient to complete the vaccination with two doses of all persons registered by April 30 if they were willing to accept the type of vaccine available Further supplies of vaccine were being distributed from time to time to keep pace with new registrations He could not at present make any statement in regard to extending the offer of vaccination to other priority groups or about the giving of third doses

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Obituary

JOHN CLARK MIDDLETON

M A, M B, B Sc Glasg, F R F P S

Dr J C Middleton, honorary consulting physician to Glasgow Royal Infirmary, who died on May 30, will long be remembered as one of the characters of the Glasgow medical school His students respected his gift for clinical teaching and his colleagues his flair for diagnosis As one of them has said, " he was terse, sometimes uncomplimentary, but always helpful "

He was born in Glasgow in 1883, the son of a schoolmaster, and educated at Whitehill School and Glasgow University He graduated M B with honours in 1907 and after holding house-appointments in Glasgow hospitals he spent several years in general practice and acted as assistant bacteriologist to the burgh of Partick In 1910 he was awarded the McCunn research scholarship and joined the staff of the university department of materia medica, where he worked under Prof Ralph Stockman In this appointment he undertook a great deal of pharmacological research and was responsible for the smooth running of the experiments undertaken by student volunteers During the 1914–18 war he served with the R A M C After he was demobilised he returned to clinical medicine and became assistant physician to the Glasgow Royal Infirmary and visiting physician to the Western Dispensary He also held a university lectureship in pharmacology and later in clinical medicine In 1926 he was appointed chief in charge of wards at the Royal Infirmary, and he held this post until he retired in 1948

A H I, who was on Middleton's staff in the 'thirties, writes

J C Middleton was burly and rubicund with very little hair, his manner was bluff with a rather mordant wit, and his language at times was distinctly salty Indeed, he was more like a prosperous farmer or ship's captain than a successful consultant physician He had a reputation for lightning diagnosis, usually made from the foot of the patient's bed Naturally he was sometimes wrong, but the frequency with which he was right was no surprise to those of us who knew his powers of acute and shrewd observation and his phenomenally retentive memory He loved controversy and even appreciated being flatly contradicted A ward round with him was a stimulating experience Afterwards he would adjourn with his staff and over coffee would light one of the pipes of which he carried at least four ready charged Amid clouds of acrid smoke, strongly tinctured with thick black tobacco, he would converse or argue on any topic under the sun His assistants and house-physicians held him in such high esteem that they founded the J C M Club whose sole function was to entertain him to dinner once a year Former residents used to assemble from far afield and he was always at his best on these occasions He has been retired for many years, but his memory is still vividly alive in his old hospital, and his passing will sadden all those of us who worked with him and knew him

GEORGE HERBERT GARLICK

M R C S, D M R E

Dr G H Garlick, director of the Anti-Tuberculosis Association Clinic, Singapore, died in Switzerland on June 6 while on his way to London to attend a conference

He was born in 1886, the son of Dr George Garlick, of Gordon Square, London He was educated at Epsom College, and studied medicine at St Mary's Hospital, qualifying in 1912 Two years later he went to Malaya, first as medical officer to a tin mine for two years and then as medical officer to the Johore Government He was appointed principal medical officer in 1930 Before he retired in 1941 he was largely responsible for designing the great new hospital at Johore Bahru He retired to a cylindrical house he had built in the outskirts of Singapore, but almost at once joined the R A M C as specialist in radiology He became a prisoner-of-war of the Japanese After the war he returned to live at the Round House, Garlick Avenue, and applied his knowledge of radiology to the campaign against tuberculosis He was a prime mover in the Anti-Tuberculosis Association, and when the Singapore clinic was opened in 1952 he became the director He married Myrtle H W I Ventris, by whom he had two daughters and a son, who is in general practice at Lakenheath in Suffolk

J K M writes

Dr Garlick will be remembered especially for his complete absence of snobbery and race-prejudice and by the Johore Bahru Hospital His house was decorated by Chinese objets d'art There was a bathing-pool beside which were tropical flowers and a life-size statue of a woman balancing on her hands Gracious and modest, he was a charming host and colleague

Diary of the Week

JUNE 22 TO 28

Monday, 23rd

UNIVERSITY COLLEGE, Gower Street, W C 1
5 P M Prof J D Fortuyn The Rhinencephalon with Special Reference to Fishes
POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W 12
4 P M Dr J F Goodwin Pulmonary Hypertension

Tuesday, 24th

INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Dr R W Riddell Less Common Mycotic Infections of the Skin

Wednesday, 25th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
5 P M *Endocrinology* Prof C H Best (Toronto) The Future in the Field of Diabetes
POSTGRADUATE MEDICAL SCHOOL
2 P M Dr R M Fry Reflections on Diagnostic Bacteriology
INSTITUTE OF DERMATOLOGY
5 30 P M Dr Desmond O'Neill Emotional Aspects of Skin Diseases (First of two lectures)
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P M Dr R W Riddell Antibacterial Agents in the Treatment of Tuberculosis

Thursday, 26th

UNIVERSITY OF LONDON
5 30 P M (London School of Hygiene and Tropical Medicine, Keppel Street, W C 1) Dr G T Pack (New York) Problem of the Pigmented Mole and Malignant Melanoma
POSTGRADUATE MEDICAL SCHOOL
4 P M Dr James Sharp Differential Diagnosis and Management of Spondylitis
INSTITUTE OF DERMATOLOGY
5 30 P M Dr I A Magnus Nickel, Chromium, and Eosin Epidermal Sensitisation

Friday, 27th

POSTGRADUATE MEDICAL SCHOOL
10 A M Mr A W Kay Pyloric Antrum and Peptic Ulceration
2 P M Dr Henry Harkins (Seattle) Surgery as Practised in Europe and the United States—a Comparison
INSTITUTE OF NEUROLOGY The National Hospital Queen Square, W C 1
5 P M Sir Macfarlane Burnet (Melbourne) Encephalitis in New Guinea
SOCIETY FOR ENDOCRINOLOGY
5 30 P M (26 Portland Place, W 1) Prof O Muhlbock (Amsterdam) Hormonal Genesis of Mammary Cancer
UNIVERSITY OF OXFORD
5 P.M (Department of Pharmacology) Prof A D Welch (Yale University) Studies of Azauracil Riboside and of Interference with the Metabolism of Pyrimidines

Notes and News

NURSES' HOURS OF DUTY

THE Minister of Health has accepted (H M [58] 45) a recommendation by the Nurses and Midwives Whitley Council that the hours of duty of hospital nurses and midwives (excluding staff in supervisory posts) should be reduced from 96 to 88 per fortnight as soon as conditions permit, and he has asked hospital boards and committees " to put in hand forthwith a complete review of the existing nursing and midwifery services and staffing arrangements in their hospitals with the object of giving effect to the recommendation to the fullest extent which local circumstances make practicable " Any increase in expenditure will have to be met by hospital authorities within the total of their authorised budget and additional funds will not be made available The Minister recognises that this may limit the extent to which boards and committees will find it possible to implement the recommendation, but he feels sure that " a good deal can be done by concerted administrative action to reduce the hours of duty of nurses and midwives below the level worked at present " The Minister hopes that boards and committees will give special attention to the work of student nurses, and try to eliminate or reduce split duties wherever possible, and to arrange that the staff as a whole plan their off-duty time well in advance

WORLD HEALTH ASSEMBLY

AT the World Health Assembly, in Minneapolis, Minnesota,[1] the W H O Committee on Programme and Budget approved the 1959 general programme of work, which reflects increased activities against malaria, venereal diseases, treponematoses, and endemo-epidemic diseases, and in public-health administration, nursing, maternal and child health, mental health, and nutrition Several delegates spoke of the need to expand and improve health statistics The committee unanimously approved a proposal sponsored by the U S A requesting the Director-General to " organise and arrange for special study of the role of the Organisation in research, and ways in which W H O might assist more adequately in stimulating and coordinating research and developing research personnel "

EXTRAMURAL MEALS

MOST of us look forward to our meals with zest, and to the patient in hospital they are often the main events of his rather dull day and a vital part of his treatment The importance of serving him with appetising, hot, nutritious meals is clear to all hospital administrators, so, too often, is the difficulty In some hospitals, especially our large mental hospitals,[2] the kitchens are saddled with antique equipment and lie at a chilling trolley ride from the outlying wards The food is cooked in bulk and much of it is at least partially prepared the day before it is eaten All these defects are often aggravated by shortage of staff But boards, management committees, and hospital officers alike are alert to make the best use of their resources, and most patients would agree that hospital food is improving

A possible innovation which is being considered by the Battersea and Putney Group H M C, at the suggestion of the South West Metropolitan R H B, is to entrust the catering to an outside industrial firm A firm, Peter Merchant Ltd, which are responsible for the catering of some hospitals in Northern Ireland and of Army units at Didcot, have visited two of the hospitals of the group (St John's Hospital, a long-stay hospital of 469 beds, and Putney Hospital, an acute hospital of 106 beds) and submitted reports on their catering and the terms on which the firm would be willing to take it over

If the scheme is accepted the firm, acting through supervisory executives visiting regularly, would instruct the catering staff in their methods of kitchen control, menu planning, and cooking, and generally supervise the department In this way they would act as the hospital's catering officer They would buy on the open market, using their national buying power and taking advantage of market fluctuations They would, therefore, need to have control of the food stores and would install a control-clerk/storekeeper This would be the only employee engaged by them to work wholetime at the hospital The rest of the staff would remain the employees of the H M C The firm would be paid an agreed annual fee for this work and would also be reimbursed for the cost of food consumed in the hospital

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[1] See *Lancet*, June 7, 1958, p 1234, *ibid* June 14, p 1286

[2] Hawes, D G H *Lancet*, 1955, i, 1214

Battersea and Putney H M C are at present studying the survey submitted by the firm, and it is hoped to make a decision shortly whether to allow the firm to take over the catering for an experimental period of not less than 6 months The objects of the experiment would be, first in importance, to test the firm's claim that, as specialists, they would be able to improve the standard of catering for the benefit of patients and staff alike, and, second, to save money if possible

GERIATRIC REABLEMENT UNIT

On May 28 Lady Wakehurst opened a new wing at the Belfast City Hospital which is to serve as an extension of the department for the care of the elderly sick

Wakehurst House, as it is to be called, has evolved from ten years' experience of the reablement of the elderly sick, and it has been specially planned for this work. Two unusual points in the design are the exercise bays and the sections for long-stay invalids On the ground-floor there are staff offices and outpatient services, including physiotherapy and occupational therapy The first and second floors have male and female 41-bed ward units respectively The ward units were planned in the belief that sooner or later all doctors and nurses must accept responsibility for some long-stay patients so as to spread the load and avoid the unhappy concentrations of chronic sick of the old days Each unit is L-shaped, the short limb is a separate 16-bed annexe with its own services, including lavatories, bath, sluice, and enema rooms, for long-stay invalids who need continuous nursing care The long limb of the L is a 25-bed reablement ward divided into four open 6-bed cubicles and one single-bed ward for critically ill or disturbed and restless patients To one side is a wide bay giving space for parallel bars, walking chair, and other facilities for daily exercise At the ward entrance is a pleasant day-space close to the kitchen at the base of the L, and there is a sun balcony wide enough to take several beds

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University of Oxford

On June 7 the following degrees were conferred

D M—John Towers
B M—P F B Owen (in absentia)

University of Cambridge

On June 7 the following degrees were conferred

M D—Angus McGregor, K E K Rowson, F D Schofield, C C D Shute

M B , B Chir—*T H Almond
M.B—R B Cole, *David Freeman, A E Holmes

* By proxy

Royal College of Physicians of London

On Tuesday, July 8, Sir Lindor Brown will give the Bertram Louis Abrahams lecture on the mode of action of sympathetic nerves On Thursday, July 10, Prof P B Medawar will give the F E Williams lecture on the biology of the ageing Both lectures will be given at the college, Pall Mall East, S W 1, at 5 P M

Royal College of Physicians of Ireland

At a meeting of the college on June 6, with Dr F J O'Donnell, the president, in the chair, the following were admitted to the fellowship

K M Hickey R J Kernohan, Patrick Logan, J P A Ryan, D S Wilson Mathuranath Bhattacharyya (in absentia)

The following were admitted as licentiates and members

M P Awon, Enda Casement, D E. Donovan, V T Greene, Conn Lucey

University of London

On May 21 the degree of M D was conferred on E J Ross

Dr William Blackwood has been appointed to the university chair of neuropathology at the Institute of Neurology

Dr Blackwood, who is 47 years of age, qualified from the University of Edinburgh in 1934 After filling house-appointments in Edinburgh at the Royal Infirmary and the Royal Hospital for Sick Children and at Inverness he became assistant pathologist at the Royal Infirmary and was awarded the Crighton research scholarship In 1938 he took the F R C.S E and in 1957 the M R C P.E In 1939 he was appointed pathologist to the Scottish Mental Hospitals' Laboratory and neuropathologist to the Royal Infirmary and Municipal Hospitals, Edinburgh In 1945 he was appointed senior lecturer in neuropathology in the University of Edinburgh In 1947 he came to London to join the staff of the National Hospital, Queen Square, as assistant pathologist, later becoming pathologist His published work includes papers on immersion foot and on diffuse cerebral sclerosis He was one of the authors of *Atlas of Neuropathology* which was published in 1949 and of the late Dr J G Greenfield's *Neuropathology* published earlier this year

Dr J N Cumings has been appointed to the university chair of chemical pathology at the Institute

Dr Cumings, who qualified from King's College Hospital in 1927, is 52 years of age After holding house-appointments at King's, he became assistant pathologist there In 1930 he took the M R C P and a year later the M D Lond In 1933 he was appointed assistant pathologist, and in 1945 clinical pathologist to the National Hospital, Queen Square He was elected F R C P in 1953 He has published papers on creatine metabolism, on hepatolenticular degeneration, and on cerebral lipids in various diseases

Dr N F Morris has been appointed to the university chair of obstetrics and gynæcology at Charing Cross Hospital Medical School

Dr N F Morris is 38 years of age and qualified from St Mary's Hospital in 1943 After holding resident appointments at St Mary's and the East Ham Memorial Hospital he joined the R A F, in which he served as a surgical specialist with the rank of squadron-leader In 1948 he returned to a registrar appointment at St Mary's and also at the East End Maternity Hospital, and in 1949 took the M D Lond and the M R.C O G Later he became senior registrar in the department of obstetrics and gynæcology, Hammersmith Hospital, where he remained until 1953 when he was appointed first assistant in the obstetrical unit at University College Hospital He took up his present post of reader in obstetrics and gynæcology at the Institute of Obstetrics and Gynæcology and consultant obstetrician and gynæcologist to Hammersmith Hospital in 1956 He has published papers on several obstetric subjects His recent studies have concerned the use of radioactive isotopes in the assessment of the effective uterine blood-flow at rest in late pregnancy and during exercise, and also during labour

Royal College of Obstetricians and Gynæcologists

On Friday, July 25, at 5 P M, at the college, Prof James Black, formerly of the University of Witwatersrand, will give the William Meredith Fletcher Shaw lecture The title of his lecture is Reminiscences of Fifty Years' Medical Practice—forty-seven of them in South Africa Tickets may be had from the secretary, 58, Queen Anne Street, London, W 1

Royal Australasian College of Physicians

At a meeting of the general body of fellows of the college held in Sydney on June 4, the following were elected and admitted to fellowship

Under article 44 Lionel Lockwood (Victoria), J A R Miles (New Zealand), J S Robertson (South Australia) *Under article 42* R A Bakewell, J D Bergin, R C S Dick, W G Gray, G P Hallwright, J A Keeling, L S A Lewis, R W Medlicott, C P Powles (New Zealand), R B Blacket, Clair Isbister, A G McManus, R D Puflett, D S Stuckey, Helen M Taylor (New South Wales) Joseph Bornstein, H N B Wettenhall (Victoria) J V Gordon, B S Hetzel (South Australia), G B V Murphy, N V Youngman (Queensland)

On June 3 the following were admitted to membership

R J Cantwell, T P Casey, R J M Coates, C O Crawford, P M Dennis F E Dreifuss, J D Frankish, Colleen A Hall, E E Hannah, H J H Hiddlestone, R O H Irvine, Dr Malcolm Watt (New Zealand), L Bernstein, R W Boden, G M Bourke, B S Clifton, H Kronenberg, L Lazarus, M A Mishkel, J G Opie W K A Paver, June M Raine F L Ritchie, W A Seldon, K A Talley, W H Wolfenden (New South Wales), R R Andrew P F Bladin, D M Danks, A P Dorevitch, J A Game, G S Hale, A D McCutcheon, F I R Martin, S Shub (Victoria), T H Beare, J R. Lawrence, R H C Rischbieth (South Australia), J M Sutherland (Queensland), B C Bignold (Western Australia) *Under article 37* M C Fowler (South Australia), R D K Reye (New South Wales)

Royal College of Surgeons of England

On June 11 a ceremony of presentation of diplomas was held, for the first time, at the college

Prof C F W Illingworth (Glasgow) and Prof F de G d'Allaines (Paris) were admitted to the honorary fellowship Prof R W Scarff, Air Vice-Marshal J C Neely, and Prof F C Wilkinson, who had been elected fellows, were formally admitted

The presentation of diplomas to those who had been successful in the examinations of the college during the past year followed Parties from each of the medical schools were presented in turn to the president for receipt of the diplomas at his hands, and some 200 diplomates were presented in this way

At a meeting of the Council on June 12, with Sir James Paterson Ross, the president, in the chair, the following were coopted to the council for the year 1958–59, representing various branches of practice

Dr John Hunt, general practice, Dr Frankis Evans, anæsthetics, Mr T Keith Lyle, ophthalmology, Mr A C H Bell, gynæcology and obstetrics, Prof D W Smithers, radiology, Mr C Gill-Carey, otolaryngology, Sir Wilfred Fish, dental surgery

Mr D Ioan-Jones and Mr T G I James were re-elected members of the court of examiners for a further three years

The Hallett prize was awarded to Miss M V Ramchandani of the University of Bombay

Diplomas of fellowship were granted to the following

G B Northcroft, Valerie M Thompson, W B Ashby, R S Sneath, F R Coffin, A E Buckle, P L C Diggory, Alan Gillespie, F J Moynihan, J M Powley, W J Pryn, D M Millar, K R Pool, R Y Calne, A R Bearn, Richard James, P S Boulter, George Hayes, John Mutch, I K Mikhail, A K Chowdhury, William Lees, K A McCluskey, K A Menon, Joan Fowler-Wright, Hilton Harrop-Griffiths, N H Harris, R H Lewis, A H Petty, Kenneth Bloor, H G Brown, T I El-Gailani, Joseph Magri, G A W Milner, R F Rohan D S Sardana, C B Walker K R Alimchandani, D S Dharmage, J L Dowse, J G Gray, G L Grigg, A C Jain, K N Khanna, M L Rajakaruna, Veluppillai Rasanayakam, G E Rousseaux, E J Williams, J A Adams, S D Chatterjee, M H Cox, J C Currie, E J England, A P Fuller, B E Hagan, A H T Hodgkinson, R A Howett, Isidore Kaplan, B H Kelham, H M Learoyd, C V Mann, J A Marston, V G Mavalankar, John Moran, D C Patel, G C Robin, I B Tait, L J Walker, J H Williams, Raphael Attard, Dudley Churchill-Davidson, J A Girling, P B Humphris S R Mitra, S K Nair, B T O'Connor, K C Perry, W D Proudman, G R Raad, M P Robinson, J F Sander, Lucas Souvlis, H H Srinivasan, Prem Virmani, N K Yong, Lakshman Das, H F Jeejeebhoy, I D Johnston, M Y D Koawavwala, M G Maguire B A Maurice, D O Sullivan, C G Paull, J G Ross, S B Singh, J R Solomon, D E Cam, R D P Craig, A R Desai, K H Langford, M B Menelaus, R P Silverton, R G Smith, J L Dawson

Lady Tata Memorial Fund

For research on leukæmia and allied diseases in the year beginning October, the trustees have made the following awards

Grants for Research Expenses —Dr M Seligmann (France), Dr M Simonsen (Denmark), Prof B Thorell (Sweden), Dr M Bessis (France), Prof G Klein (Sweden), and Dr Jan Ponten (Sweden)

Scholarships —Dr A J Therkelsen (Denmark), and Dr Aiyappan Pillai (Switzerland)

N H S Administrative and Clerical Staffs

The two sides of the Administrative and Clerical Staffs Whitley Council have agreed that as a preliminary to negotiations on the application of the Noel Hall report to senior designated grades, an independent fact-finding committee of three should be asked to report on current rates of remuneration of staffs employed on comparable work in other employment Sir Noel Hall has accepted an invitation to serve as chairman of the committee

Institute for Advancement of Medical Communication

This institute was recently formed in New York "to study and develop ways to increase the efficiency of information exchange among medical scientists, medical educators, and practising physicians" The work of the institute, which is a non-profit organisation, will be financed by grants from private foundations and from agencies, private and federal, which support medical research The charter members of the board of directors are Dr Chauncey D Leake, professor of pharmacology, Ohio State University, Dr Homer W Smith, professor of physiology, New York University, and Dr Irving S Wright, professor of clinical medicine, Cornell University Dr Richard H Orr, assistant editor of *Metabolism* and formerly medical director of Grune and Stratton, Inc, will serve as executive director The temporary headquarters of the institute are at 37, East 67th Street, New York 21, N Y

Symposium on Clinical Endocrinology

This symposium, limited to 30 consultant physicians, will be held from July 7 to 11 at the Postgraduate Medical School of London, Ducane Road, W 12 Further particulars may be had from the dean

Diamond Jubilee of the R A M C

On Wednesday, June 25, at 5 P M, at B M A House, London, W C 1, Sir Gordon Gordon-Taylor will give an oration, entitled *In Arduis Fidelis*, to commemorate the diamond jubilee of the R A M C

Snow Centenary

On June 16, the centenary of the death of John Snow, wreaths were laid on his grave in Brompton Cemetery by the president and members of the council of the Association of Anæsthetists of Great Britain and Ireland, the dean of the Faculty of Anæsthetists of the Royal College of Surgeons of England, and the presidents of the Sections of Anæsthetics and Epidemiology of the Royal Society of Medicine

The honorary degree of doctor in the faculty of science of the University of Bologna has been conferred on Sir Charles Dodds The British Ambassador attended the ceremony and the new graduate afterwards gave an address in French

The Oliver Bird Prize for 1957 has been awarded to Dr Gregory Pincus of the Worcester Foundation for Experimental Biology, Massachusetts

The Bárány jubilee medal of the University of Uppsala has been awarded to Dr C S Hallpike

The council of the Middlesex Hospital Medical School have given the Comfort Crookshank award for cancer research for 1957 to Prof Charles Huggins of the University of Chicago He will deliver a lecture at the school at 3 30 P M on Thursday, July 3, on cancer of the prostate

A meeting of the Biochemical Society will be held in the department of biochemistry of the University of Sheffield, at 2 P M on Friday, July 18

The North Western Tuberculosis Society has adopted a new constitution and altered its name to the North Western Thoracic Society

The annual general meeting and dinner of the Cambridge Graduates' Medical Club will be held at Gonville and Caius College on Friday, July 4, at 7 45 P M The Master of Gonville and Caius and the Regius Professor of Physic are dining as guests of the club Any members who have not received notice of the dinner should write to Dr T B Anderson, 1, Huntingdon Road, Cambridge

The British Standards Institution has issued a draft British standard for hospital sterilisers horizontal cylindrical steam pressure type (CY [SGC] 5522) Comments should reach the Institution, British Standards House, 2, Park Street, London, W 1, by July 4

Appointments

EASTON, A L T, M B Cantab, F R C S, M R C O G consultant obstetric and gynæcological surgeon, London Hospital

GRATTON, ANNIE R, M B Manc. school M O and assistant M O H, Middlesbrough

HIGGIE, C B, M R C S, D P H M O H, Ellesmere, Wem, and Whitchurch, and assistant county M O, Salop

MACGREGOR, G A, M D Lond, M R C P part-time consultant physician, Guildford group of hospitals

MACLEOD, R C, M D Glasg, D P H, D T M & H Sidmouth, Ottery St Mary, Axminster, Seaton, and Honiton

VAUGHAN, G F, M B Lond, M R C.P, D P M physician in child psychiatry, *Guy's Hospital, London*

Colonial Appointments

BINNS, T P, M R C S, D P H principal M O (urban health), Northern Nigeria

BOULOUX, J A F, M R C S, D L O specialist (E N T diseases), Mauritius

DIKKO, R A B, M R.C S principal M O (endemic diseases), Northern Nigeria

LOU-HING, E W, L R C P E superintendent M O (specialist), leprosarium, Chacachacare, Trinidad

LYDON, DANIEL, M B N U I senior administrative M O, Northern Nigeria

SEXTON, J P, M B Edin, D P H, D T M & H principal M O (curative services), Northern Nigeria

SHUN SHIN, MAXIME, M B Lond, D T M & H medical superintendent, Mauritius

The Lancet · Saturday 28 June 1958

THE PLACE OF THE RESEARCH INSTITUTE IN THE ADVANCE OF MEDICINE *

Sir Charles Harington
Sc D Cantab , F.R S
DIRECTOR OF THE NATIONAL INSTITUTE FOR MEDICAL RESEARCH, LONDON, N W 7

A scientist of the present day who is prepared to extend his thought beyond the range of his own activities, or even his own subject, to such matters as the general impact of scientific work on civilised human life will be likely to find himself with mixed feelings On the one hand he will be filled with pride in the achievements of science and the benefits that its applications have brought, on the other he will feel some qualms about the attendant dangers The dangers that I am thinking of are not the obvious risks of misuse of scientific potential for destructive purposes, but the more subtle dangers that are inherent in the undue dominance of any particular intellectual discipline over the trend of human thought

As the achievements of science become more striking and as their impact on the practical affairs of daily life become more manifest, it is inevitable that a feeling should develop that the powers of science are limitless Such a misconception is likely of course to prevail mostly among those who are uninstructed in science, but in so far as it exists it is bound also to have some effect on scientists themselves For both the result will be harmful the scientists will tend to lose that degree of intellectual humility which is necessary for sincere scientific effort, whilst, for the non-scientific, science will become invested with an aura of mystery that might in the end confer on it a dominance over thought as restrictive as any of the religious systems have been in the past

The avoidance of such a state of affairs must depend on an increasing knowledge of science on the part of those not actually engaged in its pursuit Only from such a dissemination of knowledge can come a rational view of science which will dispel mystique and bring about a general appreciation not only of the powers of science but of its limitations, together with a recognition of what scientific work has become today—namely, one of the learned professions

These remarks may seem to be as obvious as their relevance to my present theme is obscure The point that I am particularly seeking to emphasise, however, is the importance of recognising the extent to which scientific work of all kinds has become professionalised For all professions imply organisation, and it is one aspect of organisation in one branch of scientific work that I have undertaken to discuss

Organisation and Restraint

There will be many people who will feel some reluctance to admit the necessity of organisation for scientific work, particularly so far as basic research is concerned Whilst there can be no denial of the necessity for a high degree of organisation in scientific industry and in what is commonly regarded as applied and development research, it may well be felt that original investigation must remain a purely individual intellectual activity that can only be properly pursued in conditions of complete freedom, inconsistent with any form of organisation

Though it is still true that there are some people of rare intellectual quality who are so irked by all forms of restraint that they can produce their best efforts only when their thoughts are untrammelled by any considerations other than the pursuit of knowledge, these are in my opinion very few in number The feeling to which I have referred is based I believe on a nostalgia for the time when the body of scientific knowledge was such that one branch at least could be fully comprehended by an individual, when techniques were simple and when the practical applications of scientific research were less urgently sought after This time is past beyond recall, as scientists we are no more entitled than anyone else to eat our cake and have it, and if we desire our profession to make its proper contribution to civilisation we must accept the conditions imposed by the more highly organised society in which we have to live

A further consideration is that as time goes on the importance of the work of any one person in the total scientific effort inevitably becomes less The reasons for this change are obvious As the body of scientific knowledge grows the portion that can fall within the comprehension of any one man becomes less, and even within the field that he himself has mastered his efforts will be more and more conditioned by the work of those who have preceded him This may sound like a denial of the importance of originality, it is, of course, far from being so there can never be enough originality, but with the passage of time evidence of originality is more likely to be found in the perception of hitherto unobserved correlations of knowledge than in the conception of entirely new ideas

If it be accepted that the profession of science cannot dispense with an organisation there remains much room for discussion as to the type of organisation best suited to its particular requirements It is evident at once that, especially when we come to consider original investigation, the question is not easy to answer, for in respect of this particular type of scientific activity—and it is the activity on which in the last analysis all else depends—what we have to seek is an organisation that combines the two apparently opposing characteristics of high efficiency and minimum restraint The fact that this opposition exists is inherent in the present state of development of human beings who can still not work together efficiently in the absence of some measure of control, the less such control is imposed by authority and the more it can be replaced by the willing acceptance, if not the self-imposition, of a system of organisation the better, it seems to me that this consideration should be constantly in the minds of those whose duty it is to try to organise scientific work After all, anarchy is not synonymous with chaos, and however unrealistic the conception may at present be there could be worse ideals for the scientific profession, and indeed other professions dependent on the free play of intellect, than the ultimate approximation to a system in which order coexists with anarchy

However, such flights of fancy are ill suited to the servant of a Government organisation, and in any case the situation that faces us now and will face us for many years to come has to be considered on a practical basis

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* The Linacre lecture, delivered in the University of Cambridge on May 6, 1958

The Roots of Medical Research

So far I have spoken of scientific research in general, I now wish to narrow the discussion to the field of medical research as practised today and as likely to develop in the future Such a restriction does not imply any essential difference between medical research and other forms of scientific investigation, the advance of all forms depends on a sincere desire for increasing knowledge It is platitudinous nowadays to remark that in medical research the new light may come at the one end of the scale from laboratory studies of an apparently academic character and at the other from observation at the bedside The motivation of the medical research-worker may indeed be more complex than that of other scientists, because few even of those who work only in laboratories are not influenced from time to time by the thought that their efforts are ultimately directed to the prevention and cure of illness The emotional factor thus introduced may clearly work for good or ill it is good in so far as it inspires enthusiasm and gives direction to a man's efforts, and bad in that it may remove objectivity and lead to undue haste for practical results

So far as this country is concerned, medical research, like other forms of original scientific work, has its roots in the universities, if this term is understood to include the great centres of clinical teaching, and if we think of the outstanding medical men of the past who have made major discoveries as practising clinicians we have no reason to belittle the contribution that has come from this source It is quite vital to the intellectual life of any country that the universities should retain the place that they have hitherto occupied in the vanguard of thought, and in science this means not only inspiration in teaching but also activity in investigation, no-one is likely to dispute this, but differences of opinion may arise on the extent to which basic research in medicine should be pursued outside universities and medical schools Assuming what is indeed a self-evident fact, that without very great expansion of their resources the universities could not attempt to cover the whole field of basic research in medicine or indeed in any other scientific subject, is it better to extend university resources or to make independent provision of a different character?

The First Institute for Medical Research

The conviction that something more than the universities and medical schools was in fact needed for the advance of medical science took root in the minds of some a considerable time ago, and found expression in the establishment of such institutions as the Koch and Pasteur Institutes and our own Lister Institute These institutions, however, although broadening the basis of their work as time went on, were set up in the first instance with somewhat closely defined terms of reference, chiefly related to prevention and treatment of infective disease by inoculation, the first Institute for Medical Research founded for the development of basic research without any restriction on its field of activity was the Rockefeller Institute, and it is relevant to our theme to consider the circumstances that led to its establishment

The story of these circumstances has been told in the life of John D Rockefeller, Jr , published a year or two ago by Raymond B Fosdick, and it reveals a surprising fact—namely, that the notion of a general institute for medical research was first put forward by a man who was neither a doctor nor a scientist It was that astonishing individual Frederick T Gates, once a Baptist minister, later adviser in business and in philanthropy to the elder Rockefeller, and a man who profoundly influenced John D Rockefeller, Jr , who conceived the idea, and devoted all his missionary fervour to obtaining its acceptance

When Gates was seeking for ideas to suggest to Mr Rockefeller senior for the distribution of his rapidly increasing fortune he happened to read Osler's *Principles and Practice of Medicine* He records his enjoyment in reading the work, which he describes as one of the few scientific books possessed of literary attraction. In spite of the æsthetic satisfaction that he derived from his perusal, however, Gates was left at the end with a sense of disillusionment, if this book were the best presentation that could be made of medicine, how backward must be the scientific study of the subject, particularly in the United States at that period

Convinced that something was urgently needed to remedy this state of affairs, and recalling the success in their limited fields already achieved by the Koch Institute in Berlin and the Pasteur Institute in Paris, Gates submitted a memorandum to John D Rockefeller proposing that the latter should set up an institute for medical research No suggestion was made that the activities of the institute should be restricted to any definite lines, indeed the breadth of Gates' conception was surprising for a man with no knowledge of scientific work, as is shown by the key sentence of his memorandum " Medicine can hardly hope to become a science until it can be endowed, and qualified men enabled to give themselves to uninterrupted study and investigation, on ample salary, entirely independent of practice " This was written in 1897

Since the Rockefeller Institute was to afford the first demonstration of the role that such an organisation could play in medical research, it was well that the underlying idea of its establishment was so liberal, it was even more fortunate that the medical scientists, in particular William H Welch, who were consulted about the practical implementation of Gates' ideas were themselves men of wide vision who had the authority to insist that the work of the institute must be kept on a broad scientific basis, and must by no means be regarded as aiming at quick practical results immediately applicable to medical treatment There can be no doubt that faithful adherence to this conception of the purpose of the organisation was responsible for the great scientific reputation that it quickly built up and has since maintained

This is not the occasion for a discussion of the achievements in medical science for which workers at the Rockefeller Institute have been responsible These are matters of world repute, but for the purposes of the present argument their significance lies in the demonstration they afford that, at least in the circumstances prevailing in the United States, the institute played an important part This part is not confined to the actual scientific achievements, great as these have been, but extends to the impact of the work of the institute on the thought of those in the United States, and indeed in other countries, who were considering the means by which medicine might be most effectively advanced

The point is of some interest because it is possible in retrospect to be sceptical of the effect that the constitution of the Rockefeller Institute as such had on the scientific output of those who formed its staff in the early years of its existence

There are two reasons for this In the first place, at the time when the Rockefeller Institute was set up the interdependence of many different branches of science in the advance of medicine was not in principle recognised as it is today Secondly, the tendency existing to pursue researches under different headings by parallel and independent lines of approach was reinforced by the constitution of the staff itself As was natural at the beginning of a new venture, the men who were chosen to lead the various divisions of the institute were scientists of distinction and of established reputation in their own fields, within the institute they continued to develop their own lines of research largely in independence of their colleagues Whilst these men undoubtedly benefited by the better facilities that the institute afforded, it is arguable therefore that the same result might have been achieved by improving the conditions of their work as individuals in universities, without bringing them together under one roof

Birth of the National Institute

However this may be, there can be little doubt that the impressive example of the scientific output of the Rockefeller Institute, and of the Lister Institute in this country as the range of its effort broadened, must have carried great weight with the members of the Medical Research Committee (predecessors of the Medical Research Council) when they were engaged, just before the first world war, in formulating their policy At any rate one of their first decisions towards the implementation of this policy was to establish centralised laboratories to be staffed by full-time investigators, it was this decision that gave birth to the National Institute for Medical Research It is noteworthy that no defined limits were set to the scope of the work to be carried out in the centralised laboratories, or indeed to any work to be organised by the Medical Research Committee, other than the broad framework laid down in their general declaration of policy This declaration contained two key sentences, which I have quoted on previous occasions, but which I shall quote again now because of their immediate relevance to the functions of a research institute in the field of medicine

> "The object of the research is the extension of medical knowledge with the view of increasing our power of preserving health and preventing or combating disease But otherwise than that this is to be the guiding aim, the actual field of research is not limited and is to be wide enough to include, so far as may from time to time be found desirable, all researches bearing on health or disease, whether or not such researches have any direct or immediate bearing on any particular disease or group of diseases, provided that they are judged to be useful in promoting the attainment of the above object."

This statement continues to express the policy of the Medical Research Council, so that the evolution of the work of the Council, and particularly of the National Institute for Medical Research which I have to discuss, whether or not it is judged useful in the event, has at least not been inhibited by any undue restrictions

1920-1958

Although the decision to set up the National Institute was taken before the beginning of the first world war, and certain staff appointments were made at that time, the start of actual work was delayed by the war, and it was not until 1920 that the laboratories could be occupied, the institute has thus been in active operation for nearly forty years The initial appointments to the staff were made with the idea of bringing together a group of workers who would be able between them to carry out researches in all branches of non-clinical medical research, the same principle continues to operate at the present time At the outset this meant that the subjects to be represented were physiology and pharmacology, pathology and bacteriology, and chemistry, including biochemistry, in the emphasis that they laid on the latter subjects the Medical Research Council were ahead of their time

From its very modest beginning, when the total number of people employed must have been well under 100, the institute has grown to its present large size, in which there is a professional (i e, medically and scientifically qualified) staff of 142 and a total average population, including visiting workers, of about 550 This growth has been a continuous process, although the rate of expansion has naturally varied from time to time, having reached its maximum immediately after the last war It is important to note that expansion has never been encouraged for its own sake, it has been allowed to take place only when there has been a definite demand for extension of the work in one or other direction This means that the growth of the institute is in itself a reflection of the broadening in the basis of medical research during the last forty years Moreover the history of the institution is now long enough to justify an attempt to assess its contribution to the advance of medicine, and thus, taking it as an example, to form some judgment of the wisdom in general of devoting large resources to this particular type of development

I have no intention of trying to base this assessment on enumeration of the scientific achievements of workers at the institute I shall only speak of a specific line of investigation in so far as it serves to illustrate the advantages and disadvantages of work within a large research institute But let us first consider the more general question of planning of research

Planning of Research

It is important to keep in mind that we are thinking of research which, although it may require the application of the methods of chemistry, physics, and even mathematics, is directed towards a biological objective None would deny that in the exact sciences it is often possible in advance to define a problem with reasonable precision, to formulate the method of approach, and to reach some approximate idea of the type and number of people who are likely to be required for its solution In such a case the exercise of forethought in planning may well be rewarded by more rapid and economical attainment of the object Even here, however, where formal planning undoubtedly has its place, rigidity is at all costs to be avoided the behaviour of the materials to be employed may be predictable, but that of the research-workers is not, and any system is to be deprecated that will make it less likely for the research-worker to be on the alert for the new incidental observation which may ultimately turn out to be much more important than the project in hand

This consideration is even more to the point in biological work, where not only is the behaviour of the workers unpredictable but that of the experimental material as well The complexity of biological material is such, and the variety of the techniques required for its adequate study is so great, that it is impossible at the outset of a major research to foresee the range of work that will have to be covered Under such conditions formal planning can serve little purpose, and any attempt to apply it is likely to be restrictive and therefore deleterious On the other hand the protean nature of many biological problems implies that their solution may more readily be achieved by a suitable grouping of workers which can be increased or restricted according to the demands of the work If certain prerequisites are satisfied, the formation of such useful groupings should be easily brought about within a research institute, and indeed in the ideal case they may be expected to develop spontaneously . The prerequisites are (1) that the institute should be large enough, in the sense that the scientific staff will include men covering a sufficiently wide range of disciplines, (2) that the internal organisation should be flexible, and

(3) that personal relationships are such that members of the staff are willing, for a time at least, to set aside their individual preoccupations in order to collaborate with their colleagues

The sort of process that I have indicated could be illustrated by the development of several major researches in the National Institute for Medical Research I shall choose for my present purpose research on viruses, partly because this has been one of the more important activities of the institute throughout its history

Administrative Division but Working Contact

At the outset, when very little was known of the nature of viruses, their study was naturally regarded as an extension of bacteriology, and the first to undertake the work were men whose training had been in bacteriology and experimental pathology Owing to the peculiar properties of viruses, however, and in particular to their small size, existing technical methods soon proved inadequate, and the group was supplemented by optical research-workers who increased the range of microscopy by developing the use of ultraviolet light, and by a physical chemist who devised methods of estimating the size of viruses by the use of filtration membranes of graded porosity

Up to this stage the total scientific staff of the institute was still so small that it could be regarded as a single group, and there was no very clear demarcation into divisions Under these circumstances the physicists and chemists who joined in the virus researches could pursue their own interests, at the same time participating in the special work of the virus group By the time that the next major technical advance capable of contributing to virus research became available—namely, electron microscopy—the increasing size of the institute had necessitated its organisation into a number of divisions for administrative purposes The fact, however, that the responsibility for electron microscopy as a technique naturally fell to the division of biophysics did not in any way interfere with the fullest application of the method to the work of the division of virus research, on the contrary it encouraged the closest link between the two divisions, and this link has proved to be of much mutual benefit Similarly the period during which research on viruses has reached its present high state of development has also been the period that has seen the most rapid growth of biochemistry, particularly the descriptive and dynamic biochemistry of the cell The application of biochemical thought and technique to virus research has not been neglected and is rapidly growing in importance Here again is the basis for the links that have been formed in the institute between the division of virus research and those of chemistry and biochemistry

Virus research, then, in the particular institute that I am dealing with, involves the activities of many people The nucleus of the work is in the hands of the members of the division of virus research itself, these are men and women whose interest in viruses is primarily biological and medical, in so far as an organised team exists, they constitute the team In a subject of this sort, however, as in many other branches of medical research, the fringes of the effort may often turn out to be the growing points, and these potentially important fringes are studied, as opportunity offers, with the aid of workers in other relevant disciplines whose own primary interests may lie in quite different directions In my opinion the attempt to achieve effective working arrangements of this kind should be the principal aim of those who are responsible for the organisation of research institutes, because I believe that when they are achieved they constitute a service to scientific research not easily provided in any other sort of institution

Advantages of an Institute

On a more practical level a great advantage that a large research institute should be able to offer is the provision of the best technical facilities with considerable economy

The increasing elaboration of technical methods and the consequent increase in the cost of scientific research is only too apparent to all of us, nor is it possible always at the outset of a research programme to forecast accurately the type of equipment that will be required In a generally well-equipped institute, however, the major pieces of special apparatus will be found in one or other of the divisions where their primary use may happen to lie It is perfectly possible to have an understanding that, whilst the equipment is provided in the first place for the use of the laboratory where it is situated, it must be made available within reason to any other worker in the institute who finds himself in urgent need of it for the development of his research

Pooling of resources should ensure that no research-worker is frustrated in his work by lack of adequate technical facilities

Theoretically, of course, there is no reason why medical research, of the type that I have illustrated by reference to work on viruses, should not be developed as well or better elsewhere than in a research institute A university with first-class scientific and medical faculties will possess in all a far greater number of talented investigators than any research institute can hope to gather within its walls Similarly the total amount of technical equipment in the university will be greater The claim of the research institute to be able to render a unique service in medical research must rest therefore on the demonstration that it has some special quality which a collection of university departments cannot provide, however high may be their individual standing

I believe myself that such a quality does exist and that a basic necessity for its acquisition is the assembly under one roof of a collection of people with widely differing scientific interests but working together with a common sense of purpose It was said, I think by Alan Gregg, that a prerequisite for effective collaboration in research is that you should not have to put on your hat when you go to see the man you want to talk to There is certainly much truth in this, but there is an equally important requirement, which is that the man you consult should be ready to listen It is certainly much easier to develop an atmosphere in which effective mutual consultation can take place within a research institute than it can ever be in a university

Indeed, paradoxical as it may seem at first sight, the better the quality of individual university departments, the less easy may mutual consultation between their workers become, for high scientific quality in a university department tends to be associated with intense preoccupation with the subjects of investigation and a corresponding reluctance to divert intellectual effort to the problems of others, moreover it will inspire personal affection for and loyalty to the department itself rather than to the larger institution of which it is a part Furthermore, even given the utmost degree of friendliness and good will, the position of a member of one department entering another as a guest to make use of its valuable equipment can never be easy

Conditions of Success

Within a large research institute the divisions will of course correspond in a sense to the departments of a university faculty, and the head of a division, if he has, as he ought to have, some qualities of leadership, will naturally do his best to see that the standard of work in the laboratories under his care is as high as he can make it. On the other hand the essence of academic work is the pursuit of knowledge for its own sake without regard to practical issues; the essence of work in a research institute is pursuit of knowledge with the greatest degree of intellectual freedom that is consistent with mindfulness of the objects for which the institution was established. The difference, though subtle, is very real and is profound in its effects; for it will mean, if the spirit of the institute is as it should be, that the subjects for research in the different divisions are chosen not only for their own interest but for their potential contribution to the common effort. This in its turn will mean that the loyalties of the workers will be to the institution as a whole rather than to their local habitation within it, and thus may be prevented the growth of barriers that would otherwise form between groups of investigators with differing interests.

It goes without saying that the state of affairs that I have indicated as being desirable, and indeed in my opinion essential, if a research institute is to make its proper contribution does not come about automatically. The mere assembly under one roof of a number of able people, covering between them the required range of disciplines, is but the first small step. I have, indeed, ventured to criticise the Rockefeller Institute in its early days for the very reason that the effort put into its establishment, magnificently successful as it was in collecting men of talent, seems to have stopped at that point. Very positive action is required to carry matters further, and the responsibility for this rests on those who are called upon to direct research institutes.

I have already mentioned three prerequisites for success—namely, sufficient range of scientific competence, a flexible organisation governed by a liberal policy, and good personal relationships. The first and second of these depend on the employing organisation and the director working together, the third on the measure of success that the director may achieve in gaining the confidence of his colleagues. Even though these basic requirements are reasonably fulfilled, the need for constant vigilance remains. The tendency for groups of people with different intellectual interests to segregate from one another is always strong and must at all costs be combated within a research institute: the most effective weapon against this tendency is the development of researches involving many people with different outlooks and different approaches to the problem. Over and above this it is essential to preserve an atmosphere in which any member of the staff feels free to seek the help of any of his colleagues, and in which everything possible is done—by means of colloquia, open days, and any other available means—to spread knowledge of and interest in the work of individual laboratories through the institute as a whole. When all has been done by authority that can be done the happiness of any individual member of the staff and his usefulness depend on himself. In a large and active institute with a free atmosphere the opportunities for intellectual stimulation lie to his hand and it is for him to use them if he will. He can gain so much by varying his companions at the luncheon table and in the coffee room; he can lose so much by making no contacts outside his immediate associates.

Objections to Institutes

Having discussed some of the advantages that can, under the right conditions, be provided by research institutes, giving them a useful place in medical research, I must now consider some of the criticisms that are levelled at institutions of this kind—criticisms that are neither infrequent nor lacking in vigour.

I have already mentioned some of the dangers and difficulties inherent in research institutes, of which I have become conscious from my personal experience; but the criticisms that are commonly made from outside are of a somewhat different character. These criticisms are to some extent mutually contradictory; thus the academically minded critic finds it hard to believe that the higher flights of scientific investigation can be attained within an organisation that is subject to any sort of restriction or limitation of objective, whilst the practically minded critic sees the research institute as a hothouse for the development of the ivory-tower mentality. Again, it is said on the one hand that the staff of a research institute tends to be static and therefore inevitably to accumulate dead wood, on the other that by offering a sheltered existence with no distractions from research the institute drains the limited pool of talent of people who would be better employed in universities. These contradictions do not, however, necessarily deprive the criticisms of substance, and they must be examined.

The answer to the extreme academic objection that original investigation can flourish only in conditions of complete academic freedom is a simple one; it is contained in the record of major scientific discoveries that have come from medical research institutes in this and other countries. This statement is not merely a matter of personal opinion; it is substantiated by the opinion of the scientific community as shown by the recognition of workers in medical research institutes, internationally by the award of Nobel prizes, in this country by election to the Royal Society, and in other countries by analogous distinctions. In the light of this record it is manifestly untrue to maintain that the atmosphere of a research institute is necessarily less encouraging to original thought than that of a university.

The contrary argument that work in a research institute leads to loss of contact with reality has more cogency. If we accept the view that the maximum of intellectual freedom is an essential feature of a satisfactory institute, such an institute will attract the type of person capable of original thought, and we cannot be surprised that some workers placed in an atmosphere of this kind will become engrossed in the pursuit of their own ideas and will become totally uninterested in any practical application of their work. This must be accepted as a risk inherent in the research-institute system; the lack of practical interest on the part of the worker himself can be countered by increased watchfulness on the part of the head of his division and the director. Nor must we forget that even if there should be no perceivable practical outcome of the work, *this may nevertheless constitute a scientific advance intrinsically worth having*.

The questions of the effect of life in a research institute on the staff, and of the competitive requirements for scientific staff of research institutes and university departments, are best taken together. It is not to be denied that a danger of stagnation exists for the scientific staff of a research institute, but much can be done to combat this danger. It is also true that university departments and research institutes must draw on the same pool of talent, but here again it is possible to adopt a mutually helpful policy rather than to indulge in cut-throat competition

The danger of stagnation can be partly dealt with at the earliest stage by the conditions of employment It will be generally admitted that a career of scientific research is the least predictable of all careers for the young man setting out on it, it is an adventure, and for his employers a speculation It is therefore surely fair and reasonable that junior workers in research institutes should be employed on short-term appointments of three to five years until it is apparent that they have chosen the work for which they are fitted If this proves not to be so there is then still time for them to start another career

Stagnation of a more serious character can occur at a later stage It is a mistake to regard work in a research institute as a sheltered and unexacting occupation Economically sheltered it may be, but it can be far more exacting psychologically than many apparently more arduous forms of work This is often not apparent to an individual worker for a number of years, while his mind is most active he will welcome the unparalleled opportunity that a research institute can offer for the pursuit of his own research without any other responsibility For many men, however, and indeed in my experience for most, there comes a time when the satisfaction to be obtained from their own efforts ceases to be enough This time is critical, if a real sense of inadequacy and frustration is allowed to develop a good man may be lost, ceasing to be a useful member of the research institute, and at the same time having no heart for any other job

Here again there are ways in which this danger that besets research institutes can be met It does not follow that because a research-worker in early middle age has lost his desire to pursue research at the expense of all other activities he has therefore lost his usefulness On the contrary he may well have acquired other qualities of experience and judgment, and the capacity for imparting knowledge, that increase his potential value to society if the right work can be found for him Sometimes the problem can be solved within the research institute itself, if there exist official duties in which he can be given a share, more often, however, it is better for him to move elsewhere, and it is in this connection that ease of transfer from the staffs of research institutes to those of universities becomes so important

If such a transfer is to take place it is obviously only by good fortune that it can occur at the optimum moment both for the research institute and the university Since it is on the universities that the supply of future research-workers must depend, it seems to me self-evident that when there is an apparent conflict of interest the claim of the university must come first No research director in his senses would wish to compete with a university for the services of a man who would obviously make a good professor, even though *he may still be a most valuable* member of his scientific staff, *on the contrary, if he is wise*, he will encourage such a man to seize his new opportunity whilst he has full vigour to make use of it What I have just said is based not on armchair theory but on practical experience There are about twenty university professors of medical subjects, now or previously in office, in universities in this country and the Dominions, as well as several readers, who have earlier served as members of the staff of the National Institute for Medical Research In no case was any attempt made to dissuade the man from taking the university post, in no case did a man leave the institute worn out by his research and seeking only to subside into his professorial chair On the contrary, all these men have continued to be active investigators and by the quality of their departments they have made their full contribution to university life This is part of the record of the National Institute for Medical Research in which I personally feel great pride

The research institute, I believe, not only has a part to play in medicine as an efficient instrument for the advance of knowledge, but so far from being in destructive competition with universities, can complement their efforts, and may even have the good fortune to serve as a nursery for first-class heads of university departments The claim that the research institute can make a unique contribution rests on the assumption that its total effort will be more productive than would be the sum of the efforts of its constituent parts were these not welded into a closely knit scientific community I have tried to show how this claim can be substantiated, and at the same time I have been at some pains to point out the dangers to which research institutes are exposed and the conditions that are necessary for success The pitfalls are many and the frequency with which we fall into them is high, nevertheless the rewards of success when it does come are so great that the effort to maintain and develop institutes for medical research can surely be regarded as worthy of human endeavour

Two Unsolved Problems

Before I end there are two major unsolved problems which I must mention All that I have said refers to institutes concerned with laboratory research only We are, however, considering the place of the research institute within the framework of medicine as a whole If we agree that the laboratory research institute has its function and can under the right conditions be of great value, the question arises as to whether this value would be much enhanced by a close association with clinical work This brings in its train the second question, which is whether a strengthening of clinical research, similar to that achieved on the laboratory side, could be effected by the establishment of clinical research institutes

These two questions are far too large to be discussed at this juncture On the first I would only say that no-one who works in a laboratory institute for medical research can fail to be conscious of a defect in the present system It is indeed possible to ensure that discoveries made in the laboratory that have practical application are promptly brought into the right hands so that they may be properly applied, on the other hand it happens not infrequently that a research started as a laboratory investigation develops in such a way that observations on patients become desirable both from a scientific point of view and in order to study the application of the work to treatment of disease With all possible good will on both sides, the establishment of a fruitful laboratory-clinical collaboration at a distance offers formidable difficulties, and in the event frustration and loss of effort can undoubtedly result For this and other reasons it is tempting to suppose that a closer association of laboratory research units and clinical work would be advantageous, certainly to the laboratory workers and perhaps to the clinical investigators

It is tempting further to assume that the advantages would be enhanced if the association were with an institute for clinical research covering many different branches of medicine The success that has already been achieved by the United States National Institutes of

Health points indeed in this direction It does not follow, however, that an organisation appropriate to the special circumstances prevailing in the United States will necessarily succeed in other countries, and it seems to me that the question of the feasibility and usefulness of institutes for clinical research in general remains open Nevertheless I would like to end my lecture leaving this question in your minds It is at least worth thinking about. For if the answer is yes, we might, by forming institutes for clinical research and associating or combining them with laboratory research institutes, forge weapons for the advance of medical science more powerful than any that we now possess

EXPERIMENTAL PRODUCTION OF ENDOMYOCARDIAL FIBROSIS

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THE term "endomyocardial fibrosis" describes structural derangements of uncertain ætiology As Brigden (1957) points out, minor degrees of such derangements are common in many of the chronic forms of myocardial disease, but they are generally thought to be essentially different from the great endocardial thickening which appears to be the result of a specific disease particularly rife in Africa. Typical cases of endomyocardial fibrosis are common in Uganda (Ball et al 1955, Davies and Ball 1955), the Sudan (O'Brien 1954), and Eastern Nigeria, where allegedly 40% of the patients with heart-disease admitted to hospital have endomyocardial fibrosis (Nwokolo 1956). However, the disease is likewise not unusual in the Middle East (Bedford and Konstam 1946), and it has occasionally been observed in the United Kingdom (Hughes and Smith 1953, Evans 1949) the United States (Thomas et al 1954, Elster et al. 1955, Hoffman et al 1955), Switzerland (Loeffler 1936), and other countries The subject has been reviewed at some length by Gray (1951 and by *The Lancet* (1952)

Stemmermann (1957) described a malady under the name of "idiopathic endomyocardial necrosis" which he believed to be related to the typical endomyocardial fibrosis In his patient the cardiac lesions were associated with extensive morbid changes in the pancreas Stemmermann also obtained material, from twelve additional cases, through the Armed Forces Institute of Pathology (Washington, D C.), and noted that in seven of these there were pancreatic lesions—especially, focal necrosis of acinar tissue and necrosis of fat. Sometimes the pancreatic ducts were plugged with secretion and pancreatitis developed Stemmermann concluded that "the basic pattern of the pancreatic changes fits into the framework of the general adaptation syndrome".

Since the causal agent has never been identified, it is not certain that endomyocardial fibrosis is always a manifestation of the same disease, nor can it be proved that subendocardial necrosis represents an early stage of endomyocardial fibrosis Most investigators believe that endomyocardial fibrosis is due to some infection or nutritional deficiency, but this has not been proved, and Stemmermann (1957) expressed the opinion that, under certain conditions, any stressor agent could produce such myocardial lesions

Our interest in this lesion was aroused by the observation that, in various species of laboratory animals, predominantly subendocardial necroses can be produced at will by conjoint treatment with steroids and sodium salts This so-called electrolyte-steroid-cardiopathy characterized by necroses (E.S C.N) is sometimes accompanied by focal pancreatic necroses and pancreatitis (de Salcedo and Selye 1957)

The experimental production and prevention of the E.S C.N have recently been surveyed in a brief review (Selye 1958a) and in an extensive monograph (Selye 1958b) Suffice it therefore to point out here that, after suitable conditioning with corticoids—particularly with the highly potent 2α-methyl-9α-chlorocortisol (Me-Cl-COL)—not only electrolytes but even mere exposure to stress (hot or cold baths, surgical trauma, injections of adrenaline, noradrenaline, vasopressin, and many other drugs) can produce predominantly subendocardial necroses in the heart, and that these can be prevented by the oral administration of KCl or $MgCl_2$

In view of the great prevalence of endomyocardial fibrosis in certain parts of the world, it seemed of interest to establish whether this disease is related to the E.S C.N , because, if it is, the successful prevention of the latter by KCl and $MgCl_2$ may be a guide to the nutritional prophylaxis of clinical endomyocardial fibrosis

Experiments

Materials and Techniques

Forty female Sprague-Dawley rats with a mean initial body-weight of 98 g (range 90–107 g) were subdivided into four

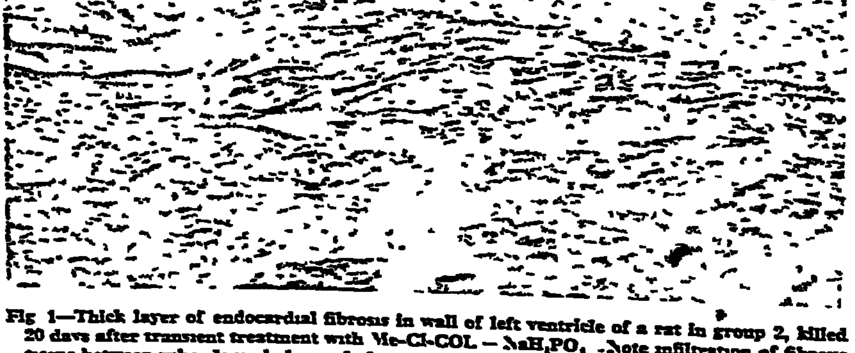

Fig 1—Thick layer of endocardial fibrosis in wall of left ventricle of a rat in group 2, killed 20 days after transient treatment with Me-Cl-COL – NaH_2PO_4 -Note infiltration of fibrous tissue between subendocardial muscle-layers. (Fuchsin. ×75)

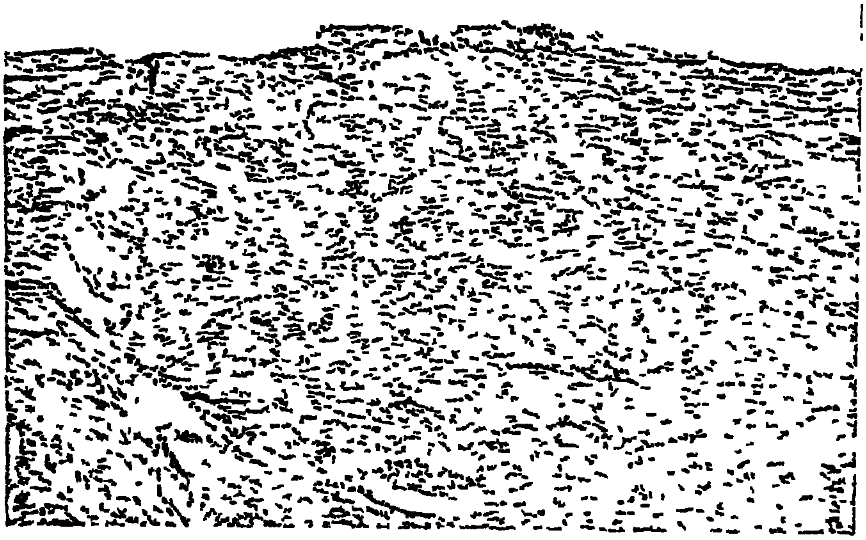

Fig 2—Comparable region of the endocardium of a rat in group 4, showing preservation of normal structure, owing to prophylactic treatment with $MgCl_2$. (Fuchsin ×75)

equal groups. All the rats were fed exclusively on 'Purina Fox Chow' (Ralston Purina Co.) throughout the period of observation. In addition, during the first 30 days they all received 1% $NaH_2PO_4 \cdot H_2O$ as their only drink, and Me-Cl-COL in the form of microcrystals of its acetate, at dose of 50 µg in 0·2 ml of water, subcutaneously, once daily. Groups 1 and 2 were not otherwise treated, whereas groups 3 and 4 received, in addition to the Me-Cl-COL+NaH_2PO_4 treatment, 1 mM of $MgCl_2 \cdot 6H_2O$ in 2 ml of water, twice daily, by stomach tube, during the first 30 days. By the 30th day two animals in group 1 and three in group 2 died with obvious manifestations of E.S.C.N. (extensive and predominantly subendocardial necroses with secondary inflammation). None of the rats in groups 3 and 4 died.

On the 30th day all the treatments were discontinued, and the survivors in groups 1 and 3 were killed. Their hearts were fixed in neutral formalin and stained with our fuchsin technique (Selye 1958b), which shows up early prenecrotic degenerative changes in myocardial muscle-fibres. The intensity of the cardiac lesions was assessed in terms of an arbitrary scale of 0–3, and it was found that on the 30th day the mean intensity of the myocardial necroses was 1·5±0·25 in the rats in group 1, whereas the animals of group 3 (which received the additional $MgCl_2$ treatment) showed no histological evidence of myocardial damage.

20 days later—i.e., 50 days after initiation of the treatment—the rats in groups 2 and 4 were killed, and their hearts were histologically examined by the same technique. The findings in these latter groups represent the principal subject of our study and will be discussed in detail below.

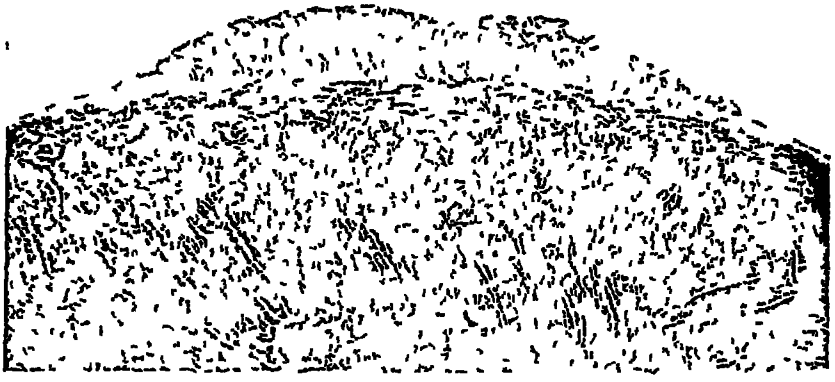

Fig 4—Circumscribed patch of fibrous pericarditis on the surface of the left ventricle of rat in group 2. Such pericardial lesions are much less common in rats so treated than is endomyocardial fibrosis. (Fuchsin ×25)

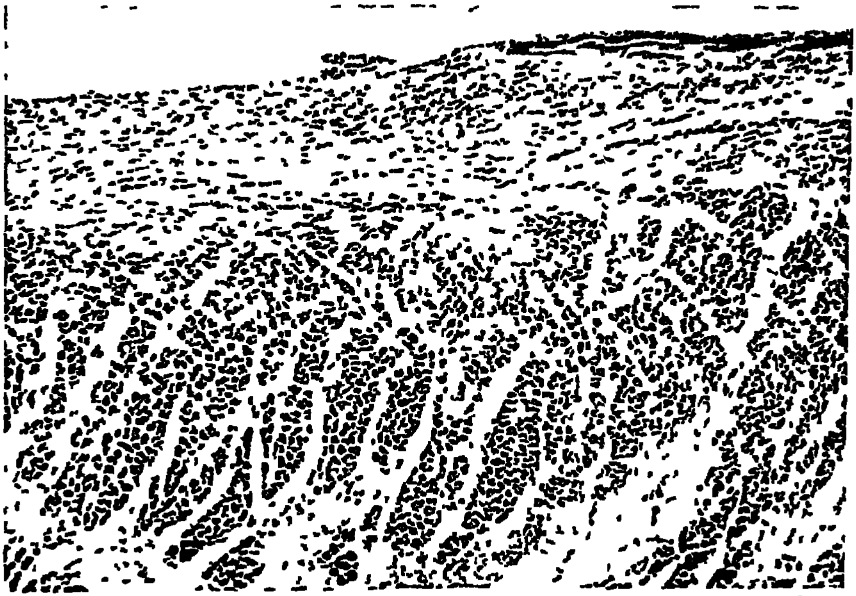

Fig 3—Particularly severe endomyocardial fibrosis in the wall of the right ventricle of a rat in group 2. (Fuchsin ×75)

Results

Two of the rats in group 2 exhibited no detectable histological change in the myocardium on the 50th day—i.e., at the end of the 20-day rest period. Apparently here, whatever minor lesions might have been present on the 30th day, when treatment was discontinued, had healed without leaving any permanent scar. However, in all of the remaining eight animals, thick layers of subendocardial fibrosis had developed in those locations where the necroses had been most plentiful in the rats of the corresponding group 1 which were killed immediately after discontinuation of treatment. In some of these rats the endocardial fibrosis was accompanied by patches of pericardial and myocardial fibrosis.

The histological appearance of these changes is illustrated in figs 1-4 The resemblance between this experimental lesion and the morbid changes found in patients who die of endomyocardial fibrosis is quite striking In the myocardium of the rats in group 4 no pathological change was detected

Discussion

It is clear from these experiments that, although small foci of myocardial necroses can disappear after discontinuation of the electrolyte-steroid treatment without leaving a trace, the larger foci of the E S C N heal by the substitution of dense connective tissue for the dead muscle-fibres Since the necroses of the E S C N tend to be localised predominantly in the subendocardial layers, the fibrosis is also most conspicuous in these regions It is evident, furthermore, that $MgCl_2$ not only prevents the development of the initial myocardial necroses but also forestalls the secondary fibrosis

We repeated this experiment on rats which received the same treatment with Me-Cl-COL plus NaH_2PO_4 for 30 days The rats that did not die spontaneously were killed after 30 days, no rest period was allowed in this experiment The results were essentially the same except that fresh subendocardial necroses and endocardial fibroses often occurred simultaneously in the same heart $MgCl_2$ again prevented the development of all myocardial changes

It remains to be seen whether electrolytes and steroids also have a decisive rôle in the development of clinical endomyocardial fibrosis, and whether $MgCl_2$ and other electrolytes that are known to prevent the E S C N (e g, KCl) could here be used to advantage as prophylactic agents Further studies will also be necessary to verify whether a high dietary intake of fats, carbohydrates, and certain Na salts which sensitise laboratory animals for the production of an E S C N (Selye 1958b), plays a part in the pathogenesis of the structurally similar spontaneous disease of man

Summary

Experiments on rats indicate that a comparatively brief period of treatment with certain corticoids, such as 2α-methyl-9α-chlorocortisol (Me-Cl-COL), plus Na salts (e g, NaH_2PO_4), produces myocardial necroses which are predominantly localised in the subendocardial layers If, in addition to this treatment, $MgCl_2$ is administered, the development of these changes is prevented

After discontinuation of treatment, the cardiac necroses thus elicited tend to heal by the formation of thick scar tissue, producing a condition resembling endomyocardial fibrosis

In rats in which these cardiac necroses were prevented by the prophylactic administration of $MgCl_2$ the secondary fibrosis did not develop

The possible clinical implications of these findings are briefly discussed

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CONTROL OF GASTRIC AND PANCREATIC SECRETION BY INHIBITION OF CARBONIC ANHYDRASE*

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THE most striking relation between the stomach and the pancreas is the way in which the gastric mucosa secreting an acid solution with a H^+-ion concentration of more than 160 mEq per litre elicits from the pancreas an alkaline fluid with a corresponding bicarbonate-ion concentration of 150 mEq per litre or more

This symmetrical integrated process has an inherent, almost æsthetic, interest, but, beyond this, clinicians have been preoccupied for the last fifty years with either controlling or suppressing this mechanism for their therapeutic ends Almost the whole of modern treatment of peptic ulcer is an attempt to abolish the stomach's secretion of hydrochloric acid, on the supposition that the ulcer is a localised area of autodigestion of gastrointestinal mucosa by hydrochloric acid

Almost the whole of therapy in acute inflammation of the pancreas is a similar effort to suppress pancreatic secretion, based on an analogous supposition that this lesion is due to localised autodigestion by pancreatic secretion

These therapeutic concepts may be wrong, but it still seems desirable to be able to control and thus to suppress the secretions of these digestive glands

If we leave aside total extirpation of the gastric glands (perhaps the ultimate aim of surgical therapy), the current useful therapeutic agents either neutralise already elaborated acid or else interfere (with variable success) with the nerves which stimulate the gastric glands A more logical approach would be direct control of the intracellular processes of secretion—inhibition at the source This is not a priori impossible, since there exist precedents for such intracellular therapeusis—e g mercurial inhibition of the renal tubular reabsorption of fluid and solutes in clinical œdema, and probenicid inhibition of the reabsorption of urates in gout

The studies of gastric and pancreatic carbonic anhydrase which are here reviewed had as their genesis the hope of establishing a safe, efficient, and practical method of controlling these digestive secretions at the cellular level This hope was not achieved, but the results of these studies indicate that such a chemotherapeutic aim is feasible and give further insight into the complex intracellular processes of digestive secretion

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* The substance of this paper was presented as the MacArthur lecture at the University of Edinburgh on May 31, 1956

Inhibition of Gastric Secretion by Inhibition of Gastric Carbonic Anhydrase

Historical

The considerable literature on gastric carbonic anhydrase was reviewed by Davenport (1946a) Here it is only necessary to recall the following points

Davenport (1939) showed that this zinc-containing enzyme was present in highest concentrations in that part of the gastric mucosa which contained the highest proportion of oxyntic cells This discovery suggested that carbon dioxide arising in these cells during metabolic processes is hydrated to carbonic acid under the catalytic influence of the enzyme, and that subsequent ionisation of carbonic acid provides hydrogen ions for gastric secretion

Inhibition of acid secretion in the dog under the influence of thiocyanate appeared to support this suggestion strongly, but Feldberg et al (1940) showed that sulphanilamide, a more potent carbonic-anhydrase inhibitor than thiocyanate, did not inhibit acid secretion, and Davenport (1946b) withdrew his theory Yet studies (Davies and Edelman 1951) on the secretion of the isolated amphibian stomach indicated that an external source of bicarbonate was needed, and that carbonic-anhydrase activity was needed to maintain high rates of secretory activity

This discrepancy between the in-vitro studies and the failure of inhibitors of carbonic anhydrase of the sulphanilamide class to inhibit gastric secretion of acid in vivo was disturbing Further, Davies and Roughton (1948), on the basis of the relative concentrations of enzyme in red blood-cells—and in gastric mucosa, had concluded that no inhibition in the living animal was to be expected, because the transport of carbon dioxide by the blood would be so seriously affected as to lead to the speedy death of the animal

Studies with Acetazolamide

Such was this unresolved situation when our interest was stimulated by the synthesis of a series of carbonic anhydrase inhibitors by Roblin and Clapp (1950) searching for more effective diuretic agents Several heterocyclic sulphonamides were created as carbonic-anhydrase inhibitors Acetazolamide received most study, but the antisecretory activity of related substances was also explored

Studies in Animals

Acid secretion was investigated in dogs fitted with vagally denervated (Haidenhain) pouches of the body of the stomach, secreting under the continuous influence of subcutaneous histamine When intravenous acetazolamide 20–60 mg per kg of body-weight was given to these animals, there followed, after 20–80 minutes, a profound fall in the rate of secretion of hydrochloric acid, ranging between 70% and 97% (average about 90%) (Janowitz et al 1952a) This persisted for from three to six hours and appeared completely reversible Most striking was the observation that this degree of inhibition of gastric carbonic anhydrase was well tolerated by the dogs Studies based on the topical application of acetazolamide to the gastric mucosa indicated that the results were due to local action on gastric carbonic anhydrase and not necessarily related to the amount of acetazolamide circulating in the plasma (Janowitz et al 1952b) This inhibition was also quite independent of alterations in the plasma-electrolyte level

Studies in Man

With some trepidation the influence of acetazolamide was investigated in man in a similar way (Janowitz et al 1957) Healthy volunteers and patients with peptic ulcers of the stomach, duodenum, or jejunum were studied during phases of unstimulated interdigestive (basal) secretion and after histamine stimulation Profound inhibition, up to complete suppression, of the secretion of hydrochloric acid was produced by the intravenous infusion of large doses (73–154 mg per kg of body-weight) of acetazolamide given in 1 to 8 hours Oral acetazolamide was ineffective, probably because such large doses were not given Although there was tingling of the extremities, anxiety, and breathlessness with doses greater than 114 mg per kg of body-weight, acetazolamide was surprisingly well tolerated

These results in animals and man indicated quite convincingly that carbonic anhydrase is intimately involved in the mechanisms of the secretion of hydrochloric acid by the mammalian stomach, and that a suitable carbonic-anhydrase inhibitor can effectively suppress this secretion in the intact organism without untoward results The extremely large doses required and, especially, the route of administration are cumbersome and restrict the therapeutic usefulness of acetazolamide In terms of our goal this method is safe and efficient but unpractical

Role of Carbonic Anhydrase in Secretion of Acid

The bulk of evidence at present indicates that the inhibition of carbonic anhydrase affects only the secretion of H^+ ions in the stomach, in contrast to its profound effects on the secretion of Na^+ and K^+ ions in the kidney Experiments, presented in preliminary form by Colcher et al (1952), lead to the conclusion that acetazolamide does not affect any H^+-K^+ or H^+-Na^+ exchange mechanisms in the stomach The role of carbonic anhydrase in gastric secretion is therefore believed to be solely concerned with the acid-secreting mechanism

Evidence based on the "alkaline tide" of the urine and on gastric arteriovenous CO_2 differences, and, especially, the studies of Davies (1951) on the metabolism of the isolated gastric mucosa indicate that, for each mole of HCl secreted into the lumen of the stomach, an equal amount of bicarbonate plus lactate appears in the nutrient (interstitial) fluid This bicarbonate is derived from plasma CO_2 and from CO_2 arising in the cell as the result of metabolic processes In both cases the CO_2 is hydrated to form carbonic acid under the catalytic influence of carbonic anhydrase, and this acid ionises to form H^+ and HCO_3^- ions

$$H_2O+CO_2 \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

During the secretion of H^+ ions at the mucosa an equimolar amount of OH^- ions is formed at the inner surface of the canaliculus of the parietal cell Accumulation of these OH^- ions, with consequent disruption of the milieu interieur of the cell, is prevented by neutralisation with HCO_3^- The present experiments indicate that the uncatalysed rate of the reaction written above is not rapid enough in the absence of carbonic anhydrase to meet the full demands of an actively secreting mucosa Consequently the rate of acid formation falls drastically when inhibitors are administered

Inhibition of Pancreatic Secretion by Inhibition of Pancreatic Carbonic Anhydrase

Historical

The sequence of events in the analysis of the role of pancreatic carbonic anhydrase has followed rather closely the gastric pattern The discovery of the enzyme in the pancreas of various animal species by Van Goor (1940) led him to postulate that the large amount of bicarbonate in pancreatic juice was ultimately derived from the hydration of CO_2 under the enzyme's influence Here again the failure of inhibitors of carbonic anhydrase of the sulphanilamide group to influence secretion significantly cast considerable doubt on its role (Tucker and Ball 1941) Shortly after our discovery that acetazolamide was effective against gastric secretion of acid Birnbaum and Hollander (1953) reported that a similar effect could be elicited in the dog's pancreas

Inhibition of Pancreatic Secretion by Acetazolamide in Man (Dreiling et al 1955)

In these studies duodenal fluid was aspirated, by continuous suction, free from gastric contamination. Pancreatic flow was stimulated by intravenous secretin 1 clinical unit per kg of body-weight because this hormone causes the pancreas to elaborate an isotonic solution of bicarbonate Acetazolamide (given as the sodium salt of 'Diamox') was infused intravenously for 1 hour between successive secretin stimulations Eighteen persons were so studied four had chronic pancreatitis, and fourteen had no disease of the pancreas With doses of 80 mg per kg of body-weight or more there was a profound inhibition of the flow of pancreatic juice and of the output of bicarbonate from the gland The effect on the output of enzyme (amylase) was much less

These results clearly showed that a suitable inhibitor of carbonic anhydrase could significantly suppress pancreatic secretion The method is safe and efficient but cumbersome Acetazolamide has been used by several workers in the treatment of external pancreatic fistulæ with apparent success (Watman 1956, Papastrat and Miller 1958)

Role of Carbonic Anhydrase in Pancreatic Secretion

Dreiling and Janowitz (1956) have shown that acetazolamide has no effect on the secretion of Na^+ or of K^+ by the human pancreas but only on the secretion of HCO_3^- ions stimulated by secretin Secretin has no carbonic-anhydrase activity and does not potentiate the action of carbonic anhydrase in man

In our present formulation the HCO_3^- ions of pancreatic fluid are derived from the hydration of CO_2 (of cellular metabolic origin in part and from plasma CO_2 in lesser part), under the influence of the enzyme Inhibition of the enzyme limits the amount of HCO_3^- ions available for secretion

In addition recent analysis indicates another function for the carbonic anhydrase (Janowitz and Dreiling 1957) It is well known that the HCO_3^- concentration of pancreatic juice is a function of the rate of secretion, varying directly, whereas the concentration of Cl^- ions varies inversely, the sum of $Cl^- + HCO_3^-$ is remarkably close to 160 mEq per litre and isotonic Under the influence of acetazolamide, although the flow and output of HCO_3^- decrease, the level of HCO_3^- tends to remain raised This has suggested a second function for the enzyme participation in a Cl^--HCO_3^- exchange in the ducts of the pancreas, which exchange may be interfered with by the carbonic-anhydrase inhibitors

Future Lines of Approach to Intracellular Inhibition

Much energy has been expended in the effort to find an "ideal antisecretory drug" with cholinergic-blocking action Experimental and clinical studies have defined the limitations of the available compounds which suppress secretion by interfering with the neural pathways for stimulation It seems clear to me that future refinements along this line are not likely to bring the "ideal" any closer in view of the widespread distribution of cholinergic-mediated neural pathways throughout the body, the quest for drugs without significant side-effects seems particularly likely to be fruitless

The present studies indicate that intracellular inhibition of secretion by digestive glands is feasible in the intact human without limiting untoward effects The carbonic-anhydrase inhibitors at present available, however, require large intravenous doses It is not unreasonable to believe that other compounds may be synthesised which are effective in smaller doses Some unpublished evidence suggests that acetazolamide and several of its derivatives may be concentrated within the parietal cells However, the distribution of carbonic anhydrase in several key organs in the body may be the limiting factor to the present experimental approach What is needed is more knowledge of the more specific intracellular enzyme-catalysed processes involved in exocrine secretion Though a considerable amount of information about overall metabolic processes within the gastric mucosa has accumulated, large gaps in our knowledge still exist The recent demonstration by Douthwaite and Booth (1956) of the inhibition of gastric secretion in man by topical application of organic mercury to the mucosa represents a relatively non-specific approach towards the same end

Summary and Conclusion

Administration to man of large doses of intravenous acetazolamide has shown two facts

(1) Carbonic anhydrase plays a vital role in man in the gastric secretion of hydrochloric acid and in the pancreatic secretion of bicarbonate

(2) Inhibition of this enzyme suppresses gastric and pancreatic secretion without untoward disturbing effects

The route of administration and dosage required for currently available carbonic-anhydrase inhibitors makes this approach unpractical at present

Inhibition of the intracellular processes of digestive secretion offers a new and feasible approach to future therapeutic research

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"Authors have deceived, by not telling how oft such a Medicine hath failed, as well as how oft it hath cured for there is no Medicine in use, but hath cured some, and there is none so excellent as to cure all, nor are all Diseases, though never so slight, curable, nor are all diseases, though never so dangerous and grievous, always and in all incurable"—WILLIAM DRAGE, *A Physical Nosonomy*, pp 4-5 London, 1665

BILIARY VESICULAR STASIS

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The commonest disorder of the biliary tract is a disorder of its motility—biliary dyskinesia Of a recent series of 200 consecutive cases investigated and treated for biliary-tract disorder, a dyskinesia was found, either alone or in association with some morphological change, in 126 The simplest and commonest form of dyskinesia is a vesicular stasis, a condition in which the gallbladder empties insufficiently This condition was present in 34 of the 126 cases of dyskinesia in this series

Biliary vesicular stasis may be divided into two main groups, hypotonic and hypertonic

Classification of Vesicular Stasis

I *Hypotonic vesicular stasis*
  1 Primary hypotonia
    (*a*) Purely functional
    (*b*) Organo-functional (i e , associated with some morphological abnormality)
  2 Secondary hypotonia
II *Hypertonic vesicular stasis*
  1 Functional or spasmodic
  2 Organic
    (*a*) Stone
    (*b*) Cystic dyskinesia
      (i) Cystic valve
      (ii) Infundibulo-colo-cysticitis
      (iii) Fibrosis of sphincter of Oddi

In the present series there were 20 cases of hypotonic vesicular stasis Chiray et al (1925) in Paris described an atonic distension of the gallbladder which was completely independent of any mechanical obstruction and constituted a definite clinical, radiological, and therapeutic entity

Hypotonic Vesicular Stasis

Hypotonic vesicular stasis is a slowly progressive disease, occasionally with exacerbations It is commoner in women and usually begins early in life The patient complains of dyspepsia, described as a heavy dull feeling in the epigastrium and below the right costal margin which comes on a quarter to half an hour after meals and remains for two to three hours These attacks last three or four days or more and appear to be initiated by the ingestion of fats, eggs, and sometimes fruit and green vegetables Discomfort and pain are felt in the epigastrium and below the right costal margin, and radiate to the dorsolumbar region and to the right scapula and interscapular regions These symptoms have usually persisted for many years before the patient comes to consultation, by which time the attacks have become more frequent and the pain more severe Appetite and weight are lost The attacks of pain, lasting half an hour or so, gradually increase in severity until the crises of pain resemble true colic Uncommonly these severe attacks may be associated with jaundice (in my series of 20 cases of hypotonic stasis, 4 had a history of jaundice, and in only 1 of these was any possible morphological cause found—a stone) and there may be a raised temperature and copious bilious vomiting Associated with these attacks of pain there is often severe headache of a migrainous type

On examination there may be tenderness on palpation below the right costal margin There will be changes in the character, amount, and flow of the gallbladder bile (which is more concentrated and flows for a longer period) obtained either by the Meltzer-Lyon test or by the chronovolumetric estimation of bile (Varela-Lopez 1950)

On cholecystography, the gallbladder is often long and flask-shaped and lies parallel to the spinal column In the erect position the density of the shadow is greatest in the fundus The form of the shadow may be distorted by the surrounding viscera It is, however, impossible to make an accurate diagnosis by means of the " classical " cholecystogram An accurate diagnosis can be made by serial cholecystography (Rose 1958), in which a series of cholecystograms (anteroposterior and lateral) are taken before and at ten-minute intervals after a fatty meal From these the volume of the gallbladder is computed and an evacuation curve is drawn The angle which the long axis of the gallbladder makes with the spine in the lateral view (angle of erection) is measured, the size of this angle is an indication of the tone and the degree of contraction of the gallbladder On serial cholecystography the cystic duct is often visible before the fatty meal is given, the gallbladder evacuates insufficiently at all stages, and there is little or no evidence of active contraction or tone of the gallbladder

It may be impossible to distinguish between a primary and a secondary stasis before operation and manometric investigation (apart from trans-parieto-hepatic vesicular puncture) The peroperative investigations are (1) measurement of the pressure within the biliary tract on a recording manometer, and (2) radiography of the biliary tract after the injection of diodone At operation the gallbladder is in many cases found to be flaccid and slightly larger than normal When pressure recordings are made, the residual pressure in the gallbladder is less than the normal 18 cm of water Peroperative radiography shows that the gallbladder is distended, elongated, and flask-shaped It evacuates easily into the common duct, which is itself hypotonic, and the opaque material flows without resistance into the duodenum and also up into the hepatic ducts The sphincter of Oddi is widely open The common duct is usually widely dilated and evacuates rapidly, the hepatic duct may also be dilated The hepatic and common ducts often form part of a large curve, or they may be sinuous

The treatment of hypotonic vesicular stasis is in the first instance medical, but eventually in most cases there must be recourse to surgery In considering the surgical treatment of hypotonic vesicular stasis it is important to emphasise that an exact diagnosis is a prerequisite and this can be obtained only by manometry and radiography at operation (Mallet-Guy and Rose 1956) It is only by these means that a primary hypotonia may be differentiated from a secondary atony of the gallbladder The surgical treatment of primary vesicular hypotonia is based on the fact that the right greater splanchnic nerve is the inhibitor nerve of the biliary tract (Mallet-Guy and Maillet 1941, Mallet-Guy and Guillet 1942) In my series of 20 cases of hypotonic vesicular stasis I performed a right splanchnicectomy in each case Each patient has been followed up by interview at intervals of one, two, three, six, and twelve months after operation and then annually In classification of the results from operative interference in my series of disorders of the biliary tract and pancreas, the following groups have been used throughout

Group Ia No symptoms and no dietary restrictions
Group Ib No symptoms but some dietary restrictions
Group II Persistence of some minor symptoms—i e , symptoms less severe than before operation (the presence of even one symptom puts the patient into this group)
Group III Persistence of some major symptoms—i e , symptoms as severe or even more severe than before operation (the presence of even one severe symptom puts the patient into this group)

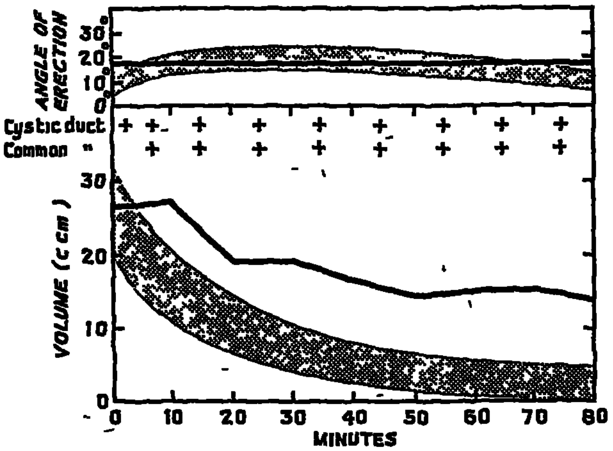

Fig 1—Serial cholecystogram, of case 1, showing a vesicular hypokinesia and a hypotonia The gallbladder is of normal size but evacuates insufficiently The angle of erection does not change throughout the examination The plus signs indicate visibility of a duct

Group IV Recurrence after a period of relief

Groups I and II are regarded as good results and III and IV as bad results

The following is a brief resumé of a typical case of hypotonic vesicular stasis

Case 1.—A woman, aged 32, weight $9^3/_4$ st *Dec 31, 1947* onset of fever (which lasted only two days), anorexia, nausea and vomiting, upper abdominal pain The liver was enlarged and tender A diagnosis of infective hepatitis was made

Jan 30, 1948 the symptoms persisted and she was readmitted, a diagnosis of duodenal ulcer was made, but the symptoms did not respond to the appropriate therapy

April 9, 1948 admitted to the teaching hospital when two other physicians and a surgeon were consulted and a diagnosis of subacute pancreatitis was made The symptoms continued, with progressive loss of weight

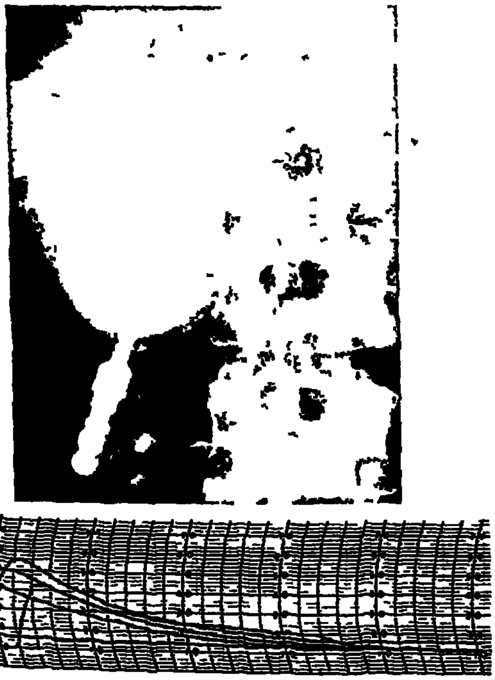

Fig 2—The operative cholecystocholangiogram of case 1, showing an atonic gallbladder with a sinuous common duct The manometric reading shows that the intravesicular pressure stabilised at 12 cm of water

July, 1948 there was a further acute attack, and readmission to hospital There was continuing loss of weight This time a pyloric ulcer was diagnosed, but this was not in accord with her symptoms Appendicectomy performed

Jan 9, 1949 referred to another teaching hospital with another acute attack of pain and dyspepsia, this time there was tenderness in the upper right abdomen and a marked intolerance of fats Weight was 7 st 6 lb After another negative cholecystogram, a second laparotomy was performed, when no abnormality other than adhesions was discovered The adhesions were divided The symptoms persisted but her weight remained at $7^1/_2$ st There were frequent migrainous bilious attacks

The patient left the district and was not seen again until *July 19, 1955*, when she returned with an acute attack of pain, one of many frequent recurring attacks There was obvious bilious pallor, tenderness below the right costal margin, and headaches At this stage the patient came under my care, a serial cholecystogram (fig 1) demonstrated vesicular stasis, probably of the primary hypotonic variety In *October, 1955*, the diagnosis was confirmed at operation (fig 2) and a right splanchnicectomy was performed

Now (two years after the operation) the patient has regained her lost weight and, apart from taking a little care with her diet, is perfectly restored to health and has taken up her full duties as a teacher She still has a few minor symptoms which in no way trouble her A further serial cholecystogram showed an improvement, but not a complete return to normal, in the motor function of the biliary tract

TABLE I—RESULTS FROM THE SURGICAL TREATMENT OF HYPOTONIC VESICULAR STASIS

Duration of follow-up (months)	Classification of results				
	Ia	Ib	II	III	IV
3					
3–6					
6–12	2		2		
12–24	9*	2	2	1	1
24–36					1†

* One of these patients had a cholecystitis only and a cholecystectomy only was performed

† This case is now recognised as one of a kink associated with a hypotonia, and has subsequently had a cholecystectomy with a good result

The condition was considerably improved by a right splanchnicectomy—so much so that the patient and her relations regard her as being cured, but as she still must take some care with her diet and must not overindulge in fats, and still has some minor symptoms, the result must be placed in group II

Table I shows the analysis of the results obtained from the surgical treatment of hypotonic vesicular stasis In the 20 cases operated on, 17 results can be regarded as good and 3 as bad There is not only symptomatic relief but also improvement in the motor function of the biliary tract in 5 cases repeat control cholecystograms were carried out several months after the operation, and in each there was an improvement in the evacuation curve, which, however, in no case returned to absolutely normal It seems reasonable, therefore, to attribute the symptomatic relief to an improvement in the function, and not, as critics have suggested, to the psychological effect of the treatment or to the enthusiasm of the doctors treating the patient[1]

In 13 of these cases of hypotonic vesicular stasis, there was no morphological abnormality, in 4 there were gallstones, in 2 a low-grade chronic cholecystitis, and in 1 cholesterosis 6 of these latter 7 cases had a cholecystectomy, and 1 had a cholecystlithotomy as well as the splanchnicectomy

Hypertonic Vesicular Stasis

Hypertonic vesicular stasis is a condition in which the gallbladder empties insufficiently on account of some obstruction to its evacuation, either functional or mechanical, and in which the intravesicular pressure is raised when it is measured by manometry at operation Of the 34 cases of vesicular stasis which form the basis of this paper 14 were of the hypertonic variety

The purely functional type is quite rare, and there were only 5 examples in this series In addition, in 2 cases there were duodenal ulcers This condition is caused by a spasm of the sphincter of Lutkens (1926) and also may be associated with a spasm of the sphincter of Oddi These spasms may be either primary (i e , no organic lesion can be demonstrated), or secondary to some organic lesion, such as a duodenal ulcer

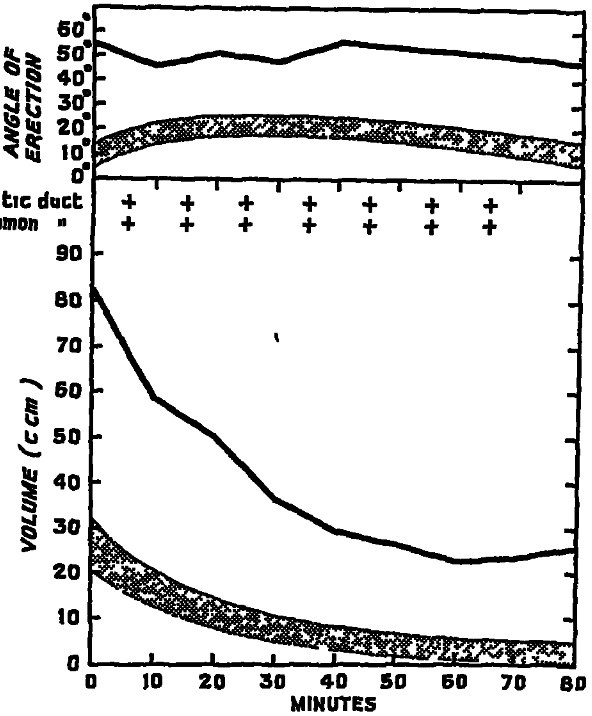

Fig 3—The serial cholecystogram of case 2, showing an abnormally large gallbladder which does not empty completely, with a high angle of erection The presumptive diagnosis is one of generalised biliary hypertonia

Clinically there is no clear-cut syndrome, and it is impossible to make an accurate diagnosis from the clinical history and physical examination alone There may be episodes of severe pain in the right hypochondrium, similar to attacks of gallstone colic, unaccompanied by an elevation of temperature Sometimes the pain is less precise and may even resemble that of a peptic ulcer Other patients complain of a typical biliary dyspepsia associated with headache and aggravated by fats Serial cholecystography shows a vesicular stasis with increased vesicular tone On the other hand, in longstanding cases a hyposystole may be present—i e , there is a slight initial contraction of the gallbladder which soon passes off Manometry at operation shows an intravesicular pressure which is above the normal of 18 cm and falls after the vagus is blocked with a local anæsthetic Radiography at operation shows a somewhat dilated gallbladder, a narrow cystic duct, and sometimes a common duct which ends like a well-sharpened pencil, indicating a coexisting spasm of the sphincter of Oddi

TABLE II—THE RESULTS OBTAINED FROM THE SURGICAL TREATMENT OF HYPERTONIC VESICULAR STASIS DUE TO SPASM OF THE SPHINCTER OF LÜTKENS

Duration of follow-up (months)	Classification of results				
	Ia	Ib	II	III	IV
3					
3–6		1	1		
6–12	2		1		
12–24	1		1		

1 case of recurrent pancreatitis with obstruction of the sphincter of Oddi, due to a combination of spasm and fibrosis, was classified as a group Ia after 12 months

Medical treatment of this condition usually fails, though some temporary improvement can be obtained by the administration of spasmolytics The surgical treatment of the purely functional type of hypertonic vesicular stasis is

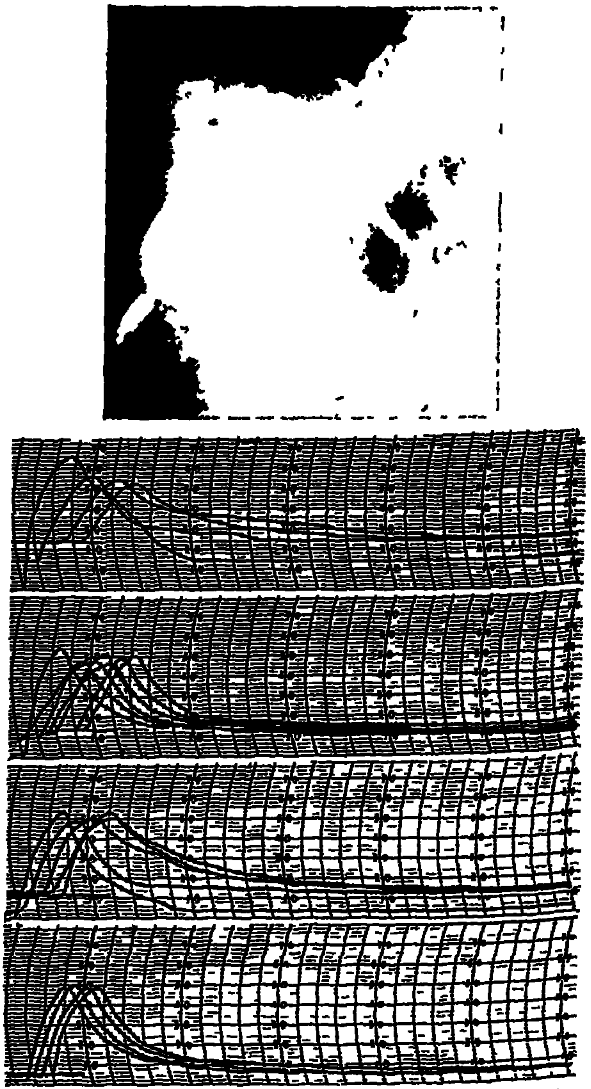

Fig 4—The operative cholecysto-cholangiogram of case 2, showing a pear-shaped gallbladder, a slightly narrowed common duct which is angulated, and a long reflux along the pancreatic duct The manometric readings show in the top graph a high intravesicular pressure, which stabilised at 24 cm of water; the second graph shows the pressure in the common duct, which stabilised at 14 cm of water The third and fourth graphs show that after blocking of the vagus the pressures stabilised at 12 cm and 6 cm. respectively, indicating a spasmodic hypertonia

to eliminate the spasm by vagal section or, as Mallet-Guy et al. (1947) advise, by cholecystectomy

Case 2.—A man, aged 43, had an eight-year history of dyspepsia, with pain across the upper abdomen radiating to both shoulders, to the left side of his chest, and into his back He had flatulence, nausea, and vomiting, which was aggravated by fatty foods Serial cholecystography (fig 3) showed a very large gallbladder which evacuated imperfectly with a high angle of erection. The presumptive diagnosis was a generalised biliary hypertonia

At operation, the gallbladder was large but otherwise appeared normal The intravesicular pressure stabilised at 24 cm of water The cholecysto-cholangiogram showed a narrow common duct and a long reflux along the pancreatic duct. The pressure within the common duct stabilised at 14 cm of water After the vagus had been blocked with local anaesthetic, the pressures stabilised at 12 cm and 6 cm respectively A diagnosis was made of spasm of both the sphincters of Lütkens and Oddi (fig 4)

A low vagotomy was performed. More than a year after his operation, the patient remains completely cured

The results of the surgical treatment of these cases are shown in detail in table II To sum up, in the 5 cases of pure spasm of the sphincter of Lütkens, good results were obtained, and both the patients with an associated duodenal ulcer were completely cured, by a vagotomy and posterior gastroenterostomy There was in addition 1 case of vesicular stasis associated with a recurring pancreatitis and an obstruction to the sphincter of Oddi by a combination of spasm and fibrosis, cholecystectomy, vagotomy, and sphincterotomy were performed, with a complete cure

A hypertonic vesicular stasis may be caused by a valve-like anatomical abnormality in the region of the junction between the cystic duct and the gallbladder This condition was first described by Schmeiden in 1920 These valve-like peculiarities and certain dysplasias of the neck of the gallbladder and the infundibulum give rise to intermittent obstruction to the evacuation of the gallbladder, which is followed by dilatation, angulation, and further obstruction The gallbladder may be divided anatomically into the fundus, the body, the neck, and the infundibulum, which leads into the cystic duct (fig 5)

It is very difficult to differentiate a valve-like deformity from a pronounced kink in the infundibulocolic region of the gallbladder, and it may be impossible to say whether a particular specimen should be classified as a valve or as a kink Such a deformity can be associated with a generalised biliary hypotonia It was thought, however, that these abnormalities should be discussed with the other causes of hypertonic vesicular stasis There is another somewhat ill-defined group of conditions which Guy Albot (1953) and his associates call infundibulo-colo-cysticitis, in which they include the various dysplasias other than kinks, valves, and acute inflammations This is a form of the so-called chronic cholecystitis which is localised to the infundibulum and neck of the gallbladder and a fibrotic condition of the cystic duct

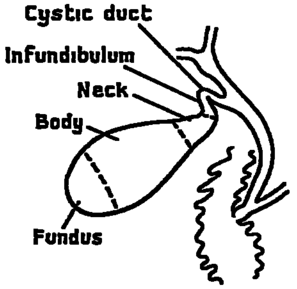

Fig 5—Anatomical regions of the gallbladder

The clinical signs and symptoms and the cholecystographic findings are variable and depend on whether the gallbladder is able to contract forcibly against the obstruction or whether the contractile power of the gallbladder has failed and a state of atony exists The most commonly found (and relatively early) condition is one in which the gallbladder still retains its power to contract. The patient complains of severe attacks of pain of short duration brought on by fatty foods Between attacks there is usually comparative freedom from pain In the early stages of this condition the serial cholecystogram shows a gallbladder which evacuates, insufficiently, with an increase in tone and contraction In most cases there is an obvious kink in the infundibulo-colic region, usually best seen on the lateral views (fig 6), but sometimes more distinctly seen on the anteroposterior view (fig 7)

Eventually the gallbladder loses its power to contract effectively against the obstruction In this late stage the

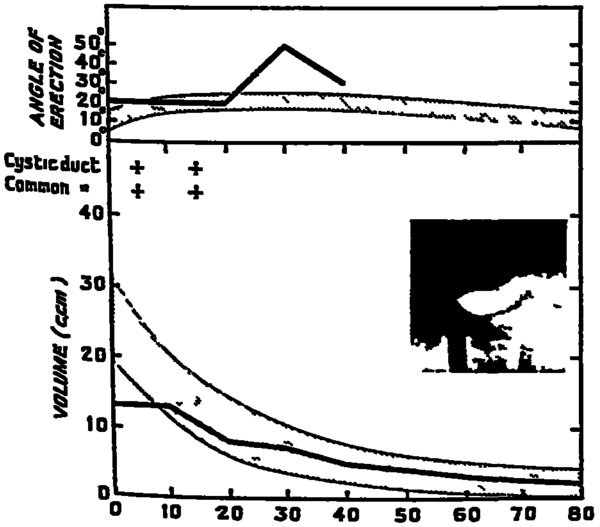

Fig 6—Serial cholecystogram, showing a small gallbladder which evacuates insufficiently, with an angle of erection which rises sharply late in the examination. The inset, a lateral view of the gallbladder shows a marked kink in the infundibulo-colic region of the gallbladder A presumptive diagnosis was made of vesicular hypokinesia associated with a kink.

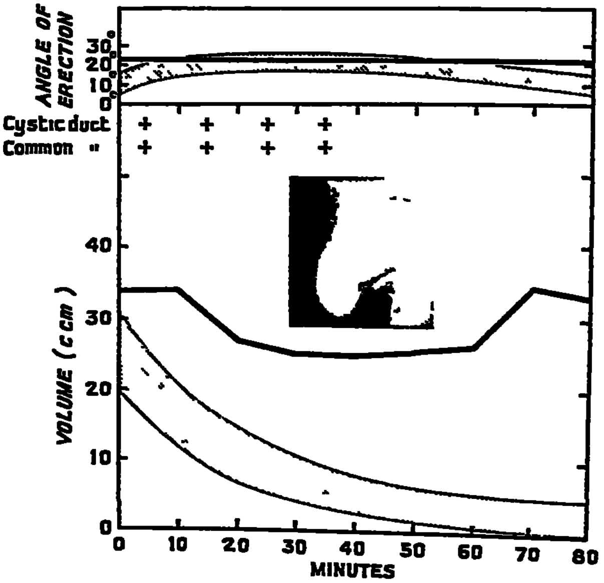

Fig 7—The serial cholecystogram of case 3, showing a vesicular hypokinesia and hypotonia associated with a kink in the infundibulo-colic region (demonstrated on the anteroposterior view) A presumptive diagnosis was made of vesicular hypotonia and hypokinesia associated with a kink.

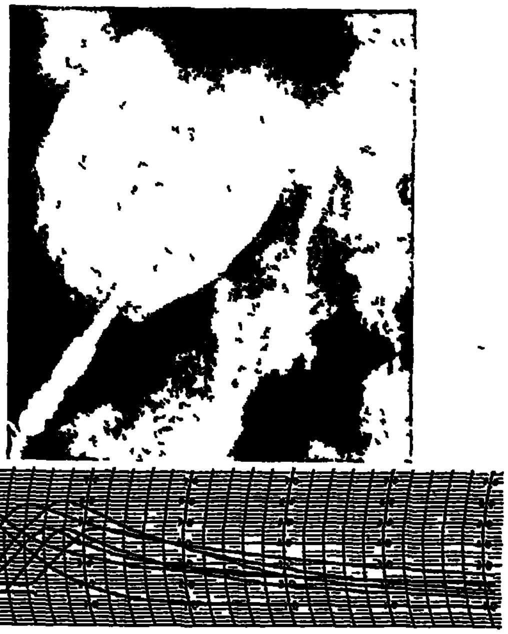

Fig 8—Operative cholecysto-cholangiogram of case 3, which shows a gallbladder slightly larger than normal, a marked infundibulo-colic kink, a long spiral valve, and a widely patent sphincter of Oddi Manometric readings show an intravesicular pressure which rose to 24 cm of water and fell to stabilise at 15 cm of water, indicating a biliary hypotonia associated with an infundibulo-colic kink

attacks of pain are replaced by a dull ache, more constant in character, in the epigastrium and radiating to the back Cholecystographically the gallbladder is atonic It is impossible as a rule at this stage to differentiate this condition from a primary hypotonic stasis This differentiation can be made only by manometry at operation (or trans-parieto-hepatic puncture of the gallbladder) In this series there were 6 patients with a valve or kink, one of which was associated with a gallstone

In the cases of a cystic valve and of infundibulo-colocysticitis, the pressure within the gallbladder is typically higher than normal and is not reduced by blocking the vagus The pressure curve of the infundibulo-colic kink is also quite characteristic in this condition the pressure curve rises to a certain level and then suddenly drops to a lower level, where it stabilises The peroperative radiographs often show a well-defined kink or tortuosity in the infundibulo-colic region The treatment of these cases is cholecystectomy, supplemented by the correction of any dystonia of the common duct which may be present

Case 3 —A woman, aged 45, had a fifteen months' history of painful dyspepsia with nausea and vomiting The pain was in the epigastrium and below the right costal margin, and radiated to both shoulders She had severe headaches with the dyspepsia, which was aggravated by fatty foods Serial cholecystography (fig 6) showed a gallbladder slightly larger than normal with gross insufficiency of evacuation The angle of erection was slightly higher than normal but did not increase during the test An obvious infundibulo-colic kink was demonstrated A presumptive diagnosis was made of a hypertonic vesicular stasis

TABLE III—RESULTS OBTAINED FROM THE SURGICAL TREATMENT OF HYPERTONIC VESICULAR STASIS DUE TO A VALVE OR AN INFUNDIBULO-COLIC KINK

Duration of follow-up (months)	Classification of results				
	Ia	Ib	II	III	IV
3			1		
3–6					
6–12	1	1			
12–24	3	1			

At operation, there were many adhesions between the under surface of the gallbladder and the surrounding viscera, these were especially dense in the region of the neck The intra vesicular pressure rose to 23 cm of water and then stabilised at 15 cm of water

The cholecysto-cholangiogram showed an infundibulo-colic kink (fig 8) The pressure within the common duct stabilised at 10 cm of water

A cholecystectomy was performed After 21 months the patient is completely cured and no longer has severe headaches

Table III gives a detailed analysis of the results, in brief all 7 patients obtained good results In 1 case there was a generalised biliary hypotonia, and a right splanchnicectomy was performed in addition to a cholecystectomy

On rare occasions a very small stone may be found in the cystic duct, causing an incomplete obstruction of the duct and thus leading to a hypertonic vesicular stasis If the obstruction is complete there will be an exclusion of the gallbladder and no gallbladder shadow on cholecystography

Summary and Conclusions

Vesicular stasis is a common disorder of the biliary tract, it was found in nearly a fifth of 200 consecutive patients who were investigated and treated There are two main types, the hypotonic and the hypertonic

The "classical" cholecystogram in this condition shows no abnormality, and an accurate diagnosis can only be made by means of serial cholecystography or trans-parieto-hepatic puncture of the gallbladder before operation, and by manometry and radiology at operation Of 34 cases of vesicular stasis treated surgically, the results were good in 31, only 3 remaining unimproved

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ACROPARÆSTHESIA IN MYXŒDEMA

A CLINICAL AND ELECTROMYOGRAPHIC STUDY

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Lethargy and slowness of movement are well known in myxœdema and widely accepted as manifestations of the effect of the hypothyroid state on the nervous system Paræsthesia, though less familiar, is mentioned by several authors (Williams 1950, Werner 1955, Soffer 1956) and nerve deafness has been described Nevertheless, no systematic clinical study of the neurological manifestations of myxœdema has been made, and the nature of many of these symptoms is assumed, without adequate evidence, to be the result of hypometabolism of the nervous system We report here clinical and experimental observations designed to test this hypothesis Preliminary results have been recorded (Murray and Simpson 1957)

Material and Methods

The present series comprises the first 35 patients observed in a general study of myxœdema

The diagnosis was made on the basis of the clinical findings, laboratory investigations, and results of therapy The tests used were estimations of the basal metabolic rate (B M R), the serum-cholesterol levels, and radio-iodine studies consisting of the measurement of the urinary excretion of radio-iodine over the first forty-eight hours and the uptake of radio-iodine by the thyroid gland over the first forty-eight hours after the dose had been given. A final diagnosis was made only after the responses of the clinical state, the B.M R , and the serum-cholesterol level to l-thyroxine sodium were known All the patients were observed for at least three months The cases were classified as minimal, mild, moderate, or severe on the basis of the general clinical picture and the B M R

11 patients were examined by an electromyographic method previously described (Simpson 1956)

The conduction velocity of the median and ulnar nerves was measured by recording the time delay of the muscle-action potential (of the abductor pollicis brevis and of the abductor digiti minimi muscles respectively) after supramaximal electrical stimulation of the nerve at elbow and wrist Coaxial needle-electrodes or silver-disc surface electrodes were used with conventional amplification and cathode-ray oscilloscope recording techniques The method and the type of record obtained are illustrated in the accompanying figure.

Results

Paræsthesia

Of the 35 consecutive patients 26 complained of paræsthesia of the fingers This was usually described as numbness or pins-and-needles and tended to occur either during certain activities—e.g , sewing, knitting, or washing clothes—or during the night, when the tingling was often sufficient to prevent sleep or to rouse the patient from sleep It was usually present on waking in the morning and passed off soon after rising Sometimes an " electric shock " sensation was noticed if an affected finger suddenly touched a hard object. Both hands were involved in 20 patients 17 patients stated that the little finger and sometimes also the ring finger were not affected by paræsthesia 7 described involvement of all their fingers, and 2 patients described numbness restricted to the ulnar side of the hand Motor symptoms were more difficult to assess Most of the patients described the clumsiness of manipulation which is well recognised in myxœdema, but 8 patients described marked loss of power of finger-thumb grip and wasting of the hand suggestive of genuine paresis Only 2 patients mentioned occasional tingling of the toes

Sensory Impairment

Evidence of sensory impairment was present in 8 cases 6 of these and 2 further cases without sensory loss showed muscle atrophy The sensory impairment was invariably on the radial side of the hand Appreciation of pinprick was reduced on the pads of the thumb, index, and middle fingers, and there was hypoæsthesia for cotton-wool on the same fingers and the radial half of the ring finger, sometimes extending proximally to the palm of the hand In 1 case the dorsum of the radial part of the hand was similarly affected, but in all the others the changes were confined to the palmar surfaces No demonstrable sensory changes were noted in the distribution area of the ulnar nerve

Motor Changes

The motor changes usually consisted in weakness and atrophy of the abductor pollicis brevis and the opponens pollicis muscles One patient had wasting of the first dorsal interosseous muscle of the right hand, and another had fasciculation of the flexor pollicis brevis All these muscles are wholly or in part supplied by the median nerve Thus all the objective sensory and motor findings pointed to a lesion of the median nerve

Electromyography

On electromyography with coaxial needle-electrodes the classical signs of partial denervation (spontaneous fibrillation and reduced motor-unit activity) were noted in 5 cases with objective weakness These manifestations were confined to the radial border of the thenar eminence, except in 1 case with fibrillation of the first dorsal interosseous muscle, which sometimes receives fibres from the median nerve (Rowntree 1949)

Conduction Velocity

Conduction velocity determined by the method described was examined in 11 cases (table I) One of these, case 1, is also case 15 of the original report on this method (Simpson 1956) Table I shows that the conduction-time of the median nerve was much increased in 3 cases, and that this increase was always due to a delay peripheral to the wrist-stimulating cathode. (The conduction-time between the two points on the nerve, obtained by subtraction, was normal in every case) In 4 other cases the conduction-time in the distal part of the median nerve was a little longer than is found in normal subjects, but the equipment used in the present work did not allow for measurement to an accuracy greater than 1 msec However, it is important to state that no unusual retardation was ever detected in the ulnar nerve, even in the first 3 cases mentioned

Carpal-tunnel Syndrome

The clinical and electromyographic findings indicate that the neuropathy is restricted to that part of the median nerve distal to the wrist, comparable in every way to the common carpal-tunnel syndrome In 1 patient acroparæsthesia of the right hand was promptly relieved by division of the flexor retinaculum six months before myxœdema was recognised When we examined her, she had moderate myxœdema Weakness of her right abductor pollicis brevis was still present She had recently begun to complain of tingling of the finger-tips of her left hand at night. No objective clinical or electromyographic changes were found The symptoms disappeared when her myxœdema responded to treatment

TABLE I—CONDUCTION VELOCITY

Case no.	Length* (cm)		Delay † (msec.)		Difference (elbow to wrist) (msec.)	Electromyography	Paræsthesia
	Elbow	Wrist	Elbow to muscle	Wrist to muscle			
1	30	6	20	14	6	Denervation	+
2	26 5	4 5	21	16	5	"	+
3	33	6	18	12	6	"	−
4	28	5	12	6	6	"	−
5	22	4	12	6	6	"	+
6	27	5	11	6	5	Normal	−
7	22	5	11	6	5	"	−
8	23	5	9	5	4	"	−
9	22	4	8	4	4	"	−
10	24	5	8	4	4	"(?)	−
11	27	6	9	4	5	"	−

* Length measured from centre of stimulating cathode on median nerve to proximal recording electrode on abductor pollicis brevis muscle

† Time interval from stimulus to nerve to onset of action potential in muscle. Normal range elbow 8–12 msec., wrist 3–5 msec.

Relation of Neuropathy to Severity of Myxœdema

No correlation was noticed between the presence of neuropathy and the severity of the myxœdema Indeed many patients with neuropathy were only considered to have mild myxœdema, whereas the most severely myxœdematous patient in the whole series had no neuropathy On the other hand, a clear relationship was established between the clinical response to treatment of the myxœdema and the disappearance of the acroparæsthesia

Follow-up

At the most recent survey 30 of the 35 patients had become euthyroid Only 3 of these 30 still noticed occasional nocturnal paræsthesia 1 had atrophy of the thenar muscles, and this was unchanged The 27 others were normal 4 patients were still graded as "mild myxœdema" 1 of these had no change in the acroparæsthesia, the 3 others still had it occasionally 1 case was still considered to be "moderately severe", with acroparæsthesia unchanged

TABLE II—RELATION OF BODY-WEIGHT TO ACROPARÆSTHESIA

Case no	Weight (kg)	Change in weight	B M R (%)	Acro-par-æsthesia	Comment
12	77 8 70 5 75 0 67 0	−7 3 +4 5 −8 0	−31 +12 − 9 +21	++ − + −	Myxœdema relapsed when treatment was changed, with transient return of acroparæsthesia
2	77 3 68 7	−8 6	−36 − 2	++ −	Complete remission and restoration of conduction velocity (table III)
13	81 4 75 0	−6 4	−26 + 1	++ −	Rapid response to triiodothyronine (3 weeks), no relapse
6	63 6 61 8	−1 8	−28 − 3	− −	Severe myxœdema, but patient not overweight
4	85 0 82 7	−2 3	− 5 +21	++ +	Good metabolic response but remains overweight
8	68 2 67 2	−1 0	−30 − 8	+ +	Ditto
14	78 6 72 7	−5 9	−17 + 3	++ +	Ditto
15	64 0 66 3	+2 3	− −	+ +	Myxœdema improved, but patient gained weight

One of the histories is particularly interesting (table II, case 12)

Bilateral median paræsthesia had been very persistent in a woman with moderate myxœdema When this was treated with triiodothyronine, the neuropathy disappeared When treatment was changed to thyroxine, she had a temporary relapse, during which paræsthesia returned, but it finally disappeared when control of myxœdema was regained

Body-weight

The patient's weight appears to us to be of greater significance than the degree of hypothyroidism Selected cases illustrating this trend are shown in table II, which shows that severe myxœdema without excessive body-weight is not accompanied by acroparæsthesia (case 6), whereas very slightly myxœdematous patients have this symptom if they are overweight (case 4), and good metabolic response to treatment is not associated with recovery from acroparæsthesia if there is not significant loss of weight (cases 4, 8, and 14) One man (case 13) with severe myxœdema and bilateral median paræsthesia, with clumsiness of the hands, lost 6 4 kg weight in three weeks when treated intensively with triiodothyronine Within that period his paræsthesiæ disappeared and have not returned

TABLE III—RESTORATION OF NERVE-CONDUCTION VELOCITY

Date	Weight (kg)	Length (cm)		Delay (msec)		Difference (elbow to wrist) (msec)
		Elbow	Wrist	Elbow to muscle	Wrist to muscle	
Aug 21, 1956	77 2	26 5	4 5	21	16	5
Jan 23, 1957	68 6	25 5	5	12	7 5	4 5

Case 2 before and after treatment Recovery of conduction velocity is not yet complete

Restoration of Nerve-conduction Velocity

This was seen in one of the most severely affected patients (case 2)

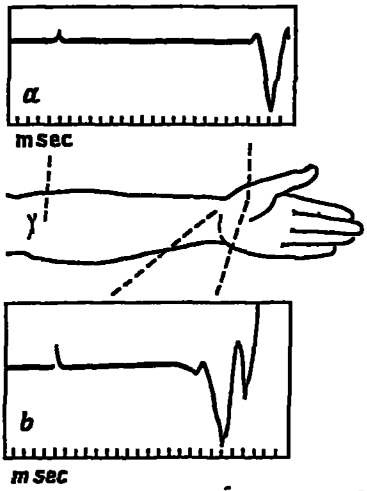
The patient, a woman with "moderately severe" myxœdema, had bilateral paræsthesia and sensory loss of median distribution in her right hand Movements of her thumbs were clumsy but quite powerful No obvious wasting was present, but electromyography disclosed partial denervation of the right abductor pollicis brevis muscle Conduction velocity of the right median nerve distal to the proximal palmar crease was greatly diminished, though the velocity above this point was normal (table I) Treatment with thyroxine achieved clinical cure of myxœdema, the patient lost 8 6 kg, the median-nerve symptoms disappeared, and the conduction velocity returned to normal (table III)

Discussion

Peripheral-nerve disorders in myxœdema are not widely recognised The standard textbooks on neurology (Wilson 1955, Brain 1955) list myxœdema among the causes of peripheral neuritis, but no references to original papers are given, and it is not clear whether the tabulation represents the personal experience of the writers From the context it appears that generalised peripheral neuritis is intended rather than the more restricted syndrome termed "acroparæsthesia", which is, by usage, confined to paræsthesiæ of the hands (Kremer et al 1953) Paræsthesiæ of the hands in myxœdematous patients have been mentioned by some workers (Williams 1950, Werner 1955, Soffer 1956) but have not been studied in detail

The diagnosis is doubtful in the 2 cases reported by Currier and Brink (1948) to show correlation between multiple neuritis and hypothyroidism

Their first case developed a neuropathy ten years after thyroidectomy The B M R was −27%, but the blood-cholesterol was 80 mg per 100 ml, there was also a history of macrocytic anæmia Free HCl was present in the gastric juice, but steatorrhœa was not excluded Treatment with thyroid extract caused "little change", but there was delayed improvement In their second case myxœdema was diagnosed despite a B M R of −8%, because the yellow colour of the patient's hands was considered characteristic of carotenæmia, which earlier workers (cited by Currier and Brink) believed to indicate hypothyroidism This patient had an acute paresis of all limbs,



Case 3—Shock artefact shows time of stimulus at cathode on median nerve at *a*, elbow, *b*, wrist After delay due to conduction along nerve this is followed by muscle-action potential recorded by coaxial needle-electrode in abductor pollicis brevis muscle

with retention of tendon-reflexes and a zone of sensory deficit along the dorsal spine. This unusual syndrome was regarded by Currier and Brink as a manifestation of polyneuritis, but they admit that neither of their cases conforms to accepted criteria.

We have therefore searched for peripheral-nerve symptoms in all patients found to be myxœdematous. Few patients presented with it as their primary complaint, but it was spontaneously mentioned by several others. On questioning it became clear that in most of them the paræsthesiæ were indeed distressing, but the degree of disability was difficult to assess in view of the mental lethargy and the predominance of more troublesome complaints, such as intolerance of cold. The mental state also made the determination of sensory disturbances difficult in many patients.

Our interest was intensified by the fact that one of us was studying the effects of metabolic disturbances on nerve conduction in man. It seemed a reasonable hypothesis that some of the slowness and clumsiness of the patient with myxœdema might be due to diminution of the rate of conduction of the nerve impulse. We were aware of the work of Lambert et al. (1951) showing that the twitch of an indirectly stimulated muscle was greatly slowed in myxœdema, and that this was responsible for "pseudomyotonic" tendon-reflexes. These workers had reported that the action potential elicited reflexly by tapping a tendon appeared after a normal delay, suggesting that the reflex arc, and hence the nerve-fibres, conducted with normal velocity. These studies, however, were made on the lower limbs, and our preliminary clinical investigations suggested that changes appeared earliest in the upper limbs, if indeed they were not confined to them.

Our clinical investigation disclosed a high incidence of symptomatic disturbances and many demonstrable motor and sensory changes confined to the hands. Sensory loss occurred exclusively in the part of one or both hands supplied by the median nerve. Motor phenomena involved only muscles in the hand supplied completely or in part by the median nerve. A few patients complained of paræsthesiæ involving the ulnar part of the hand. It is impossible to be dogmatic about subjective phenomena, but it should be noted that similar complaints are common in the carpal-tunnel syndrome (Kremer et al. 1953).

The clinical findings thus indicated a lesion of the median nerve in its distal part in all respects similar to that recognised as the carpal-tunnel syndrome. It was therefore of interest to find that the electromyographic study revealed that some of these patients had slowing of conduction restricted to the most peripheral part of the median nerve but not involving the ulnar nerve. The changes are those described in the carpal-tunnel syndrome (Simpson 1956).

The original hypothesis of diminished conduction of nerve due to hypometabolism was not confirmed. For this reason it is of some importance to examine this unexpectedly high incidence of carpal-tunnel syndrome in myxœdema, particularly as it has been reported in other endocrine disturbances—e.g., acromegaly (Kellgren et al. 1952) and pregnancy (Kremer et al. 1953). Further evidence that metabolic change in the nerve does not provide an explanation is seen in the lack of correlation between acroparæsthesia and the severity of myxœdema and in the relief obtained by operation in one case. On the other hand, there is a strong possibility that the syndrome is related to weight gain, and hence presumably to myxœdematous tissue under the flexor retinaculum at the wrist. Similar accumulation of soft tissue (with the possible addition of bone in acromegaly) could be postulated in each of the endocrine causes of the syndrome.

Summary

Median-nerve acroparæsthesiæ and paresis are common in myxœdema.

There is no generalised abnormality of nerve conduction, but slowed conduction in median nerve at the wrist can often be demonstrated.

The clinical and experimental findings indicate compression of the median nerves in the carpal tunnels.

The paræsthesiæ and paresis are probably caused by accumulation of myxœdematous tissue under the flexor retinaculum of the wrist.

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GRAVITATIONAL LEG ULCERS IN THE ELDERLY *

STANLEY RIVLIN
M.R.C.S.

SURGEON TO THE LONDON VARICOSE CLINIC

BOTH patients and their doctors tend to accept the presence of an ulcerated leg with a grim and determined stoicism born of years of unsuccessful treatment. In the elderly this attitude of mind may be so far fixed that the patient will not seek treatment again unless given the stimulus of renewed hope.

This paper is based on a study of 200 consecutive cases of gravitational ulceration, 93 of them in patients over 60 years of age. "Gravitational ulcer" is a generic term, devised by Dickson Wright (1931) to emphasise the production of œdema in the lower limb when the heart is at a higher level than the leg. For the leg to become œdematous, the patient does not have to be *erect*, as is sometimes supposed; a man sitting up in bed will not lose his pitting œdema, and it may not disappear even if he lies down. This is why so many ulcers fail to heal in bed. It is not until the foot of the bed is raised 9 in. (the patient lying flat with one pillow for the head) that the heart can be guaranteed to be below the level of the leg and a gravitational ulcer equally guaranteed to heal. But this is a method to be avoided, wherever possible, in the elderly.

Of the 200 ulcers, 150 (75%) were classified as varicose, 30 (15%) as post-thrombotic, and 20 (10%) as miscellaneous. Œdema is the common final cause in all three groups. Varicose veins produce œdema by an alteration in tissue-fluid hydrostatics due to an increase in average venular pressure (Rivlin 1956). So also does deep venous thrombosis. Miscellaneous ulcers arise in lower limbs whose œdema is due to the failure of weakened or poorly used calf muscles to maintain an adequate venous return (e.g., hemiplegia, rheumatoid arthritis, arthritis of hip and knee).

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* Based on a paper read before the Medical Society for the Care of the Elderly, Oct. 12, 1957.

I should like to see inscribed over the portal of all varicose clinics the slogan *œdema rots*, for this is the clue to the healing of leg ulcers

Diagnosis

Accurate diagnosis is essential not only for prognosis but also to make possible a comparison of results from different centres Unfortunately there is tremendous variation in the criteria of diagnosis In busy clinics there is little time for history-taking and examination Ball and Phear (1957) reported no less than 16% of their leg ulcers as "cause unknown", while Dodd et al (1957), in the hospital records of 51 out of 174 patients, found no note as to *whether or not* there was a history of deep thrombosis

In the London Varicose Clinic, forty-five minutes per patient is allowed for the initial interview The history-taking alone may be very tedious, for many of these patients have a long and involved story to tell, but complete assessment is well worth while, for in almost every case it enables an accurate diagnosis to be made, the prognosis to be determined, and the patient told what the future holds Treatment sessions are held separately

I estimate that out of every ten gravitational ulcers about six are due to simple varicose veins, three to venous thrombosis, and one to impaired leg-muscle action, R A King (personal communication) agrees with these ratios, but Dodd et al (1957) assume "most cases" to be post-thrombotic in nature, while Ball and Phear (1957) find 32% to be varicose

Treatment

Since a chronic gravitational ulcer needs œdema for its perpetuation, all treatment must aim at abolishing œdema

Bed

The simplest and most direct way of banishing œdema is to tip the patient so that her legs are higher than her heart, and this method has to be used for those who cannot walk But unless there is continuous supervision by an enthusiastic physiotherapist who regards it as her duty to prevent her patient from stiffening up in bed, we are liable to end up with a healed ulcer in a desiccated mummy The patient too—aided by non-stupefying analgesics—must play her part, persevering with exercise *at the ankle-joints to revive calf-muscle action* This is far from "bed rest" indeed, the patient must work very hard Details must be strictly adhered to A patient is allowed out of bed *only* to the toilet—a quick visit to the closet generates less œdema than a struggle with a bedpan—and may sit up in bed *only* for meals, thereafter lying down immediately Apart from these five occasions she must lie with one pillow for the head She may lie in any attitude she pleases, provided that the foot of her bed is permanently raised on 9 in blocks

Having said this, I must add that I used this method in only 3 of the 200 cases 2 had severe rheumatoid arthritis and 1 hemiplegia It is of course *not* a simple method The patients have to be visited two or three times a week, they cannot work, their morale has to be maintained, and above all they learn very little that will help them in the future *In the elderly, moreover, it is* the very antithesis of modern functional reablement

Ambulation

Bandaging *alone* will not heal many ulcers, but ambulation will do so, provided the patient can walk in comfort This explains why faith-healers achieve occasional successes and also why some ulcers heal, without our help, when the local nerve-ending is destroyed, pain ceases, and ambulation is resumed It is also the basis of the 19th-century procedure of sectioning the saphenous-nerve, which at one time had quite a vogue (Hilton 1863)

Bandaging speeds up the healing process tremendously by taking up the slack left by the vanishing œdema and preventing its return in periods of inactivity, and for this reason bandaging is essential But it is ambulation, not the bandage, that heals the ulcer

Re-education

First and foremost therefore the emphasis in treatment is placed on ambulation and normal use of the limb We ask the patients, "Which do you prefer, walking or standing?" Without a moment's hesitation they reply "walking", and this is the key to their understanding of their own problem, for if they place a hand on their own calf while flexing and extending their ankle, they can immediately appreciate (as one explains it to them) that walking is more comfortable than standing because the action of the calf muscles pumps out some of the "swelling" from their leg From that point they can be led to see that walking will prevent their leg from becoming tight and swollen in the bandage We explain to them that rest does far more harm than good Sitting in a chair with the legs up on a stool *impairs* venous return and is harmful At this stage a further dawn of recognition takes place, and they say "It's a funny thing, I always felt that rest made my leg more uncomfortable, but everyone told me to do it so I thought it *must* be right"

And now comes the most difficult and yet the most vital step of all, namely to insist that lace-up shoes are worn *all* the time and slippers completely abandoned These patients nearly all wear slippers or loose open shoes in the house, and if possible, at work It must be drummed into them over and over again that unless they wear lace-up shoes walking does not give them anything like full ankle movement, and hence full venous return, and that consequently much of the benefit of the treatment will be lost Good shoes make all the difference between a comfortable and uncomfortable bandage, and consequently between a fully mobile and semi-invalid patient After this it is easy to make them move their ankles while sitting, to point out the disadvantage of sitting close to the fire (which most of them have discovered for themselves), to warn against sitting with the legs crossed (because this retards venous return), and to arrange for the foot of the bed to be raised 9 in *if the ulcer is post-thrombotic* Finally they are given a card with the rules

USE YOUR LEG NORMALLY WHILST
UNDER BANDAGE TREATMENT

1 *Avoid standing STILL Take a few steps whenever possible*
2 *Wear lace-up Shoes, never slippers, in the house If your feet feel hot and tired at the end of the day, change into another pair of SHOES not Slippers*
3 *Do NOT sit with your legs crossed*
4 *Do NOT sit with your legs out in front of you on a stool*
5 *Sit NORMALLY but move your ankles up and down (as if beating time to music) every now and again*
6 WALK AS MUCH AS YOU PLEASE
7 Do not sit close to the fire
8 Never bath in the morning—only at night
*9 Raise foot of bed on 9in blocks

**Strike out if this does not apply*

clearly printed on it, not only to remind themselves of their new mode of life, but also to confront their well-meaning friends who say "but surely you ought to be resting your bad leg"

The Bandage

Non-irritating

At first I followed Dickson Wright's (1929) advice and used 'Elastoplast', with success (Rivlin 1951) But if skin irritation is to be avoided, we need an adhesive bandage that will not provoke a reaction from the dermis 'Poroplast' (Scholl) is well on the way to being such a bandage But, so far as ulcerated legs are concerned, the porosity on which the manufacturers laid stress, has made comparatively little difference, because the ratio of skin pores to bandage pores is so overwhelming that the degree of ventilation provided can have little physiological effect When Russell and Thorne (1955) compared porous elastoplast with equally porous poroplast they obtained better results with the latter because it contained virtually none of the irritating resins or rubbers which produce skin reactions

Adhesive

In my view it is essential that leg bandages should be adhesive Ulcers can, of course, be healed with non-sticky bandages, but most patients find that the tendency to take a peep at the ulcer, and perhaps apply a favourite salve, is almost irresistible But what matters even more is that a large proportion of patients can never be trained (or only at great cost in energy and time) to bandage their own legs efficiently they may make a passable show at it, but they do not take up the slack of their vanishing œdema nearly as efficiently as a professionally applied flexible adhesive bandage Hence, if the bandage is non-adhesive, their ulcers heal far more slowly, and they are far more likely to become dispirited

Flexible or Elastic?

The difference between "flexible" and "elastic" adhesive bandages is one of degree only, but it is important "Elasticity" refers to "stretch and regain" properties, but in fact in elastic bandages the stretch is *greater* than the regain, and after a fortnight's wear—which is the standard time—the bandage is undoubtedly looser than when first applied, and does not take up the slack of the vanishing œdema Towards the end of its clinical life it is not completely efficient The "elastic" adhesive bandage is said to have a massaging action as the patient walks, but the "massage" comes from within, not from without The muscle movement requires only a moderate degree of "give" in the bandage, in other words it is the *flexible* adhesive bandage, which has a moderate degree of stretch and in fact is no looser at the end of a fortnight than when first applied, that possesses the most desirable qualities for bandaging ulcerated legs

Paste Under-bandage

At the London Varicose Clinic, local skin irritation has been much reduced since the introduction of Scholl's 3 in flexible adhesive bandage (poroplast) I now see only 3 cases of irritation and allergy each year, as opposed to 50 or 60 previously But I still use a paste under-bandage on the leg—for two reasons

1 With a paste bandage underneath, irritation is further lessened and can be spotted and dealt with long before any generalised allergic reaction takes place (A paste bandage does not protect a sensitive skin against bandages with irritating components, for these penetrate it)

2 I have a clinical impression that some ulcers heal even faster as a result of the ingredients embodied in the paste bandages—usually some combination of zinc paste and ichthammol, urethane, and calomine

I personally prefer the 'Dalzoband no 4' for ease of application, though I believe that other ichthammol bandages are just as efficient Unlike this, the unna's paste type of bandage dries very hard, producing uncomfortable ridges on the skin

Application of Bandages

The art of bandaging is learnt only by apprenticeship Ideally, bandage technicians for varicose clinics should be specifically trained, as are orthopædic plaster technicians at the moment. The following methods are now in use at the London Varicose Clinic

Paste Under-bandage (Dalzoband No 4—one bandage)

The paste bandage is applied in almost the same manner as a plaster-of-paris bandage, in that the ultimate aim is a *smooth* case (remember any ruckle will be bandaged into the limb) of equal thickness throughout, stretching from the bend of the knee to the base of the toes We prefer to start at the bend of the knee, bandaging clockwise irrespective of whether it is the right or left leg, *laying* the bandage gently on without any pressure whatever Each turn overlaps the previous one by at least a half its width so that the bandage nowhere appears transparent We do *not* (as the manufacturer directs) "let the bandage go where it wishes", but—with a persuasive hand pleating over any fullness in the turns—we guide it in a circular manner down the leg The circular turns continue around the ankle to the toes, eschewing the figure-of-eight, which is liable to produce local constriction

Flexible Adhesive Outer-bandage (Scholl's 3 in —one and a half bandages)

Before the top bandage is applied, a strip of the adhesive bandage must be laid along the front of the limb from tibial tubercle to toes (fig 1) If this is not done the edges of the turns of the top bandage will cut into the leg at the front of the ankle and over the shin, producing discomfort, limitation in walking, and œdema This bandage begins at the base of the toes and ends at the bend of the knee The circular turns are laid on *firmly* and *evenly*, each overlapping the next by just over a half The method of circumnavigating the ankle is important, for on this depends much of the comfort of the bandage arrange the turns so that the lower edge of the fifth turn lies exactly on the point of the heel (fig 2), and then make the lower edge of the *following* turn lie at the junction of the tendo achillis with the calcaneum Where the bandage does not fit, pinch it together and cut it off Then continue clockwise up the leg to the knee

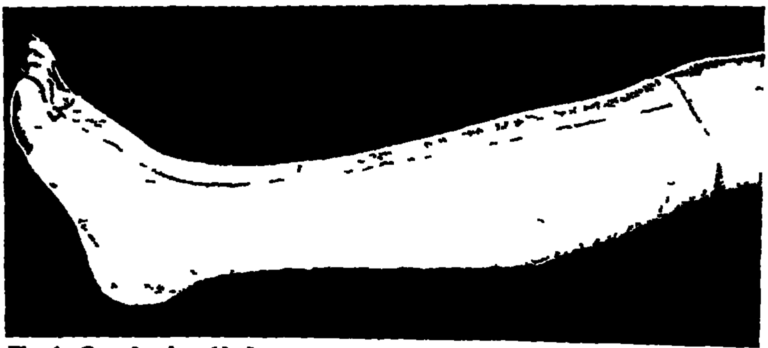

Fig 1—Completed ruckle-free paste under-bandage The longitudinal anterior strip of flexible adhesive bandage prevents the outer bandage from cutting in to ankle or shin

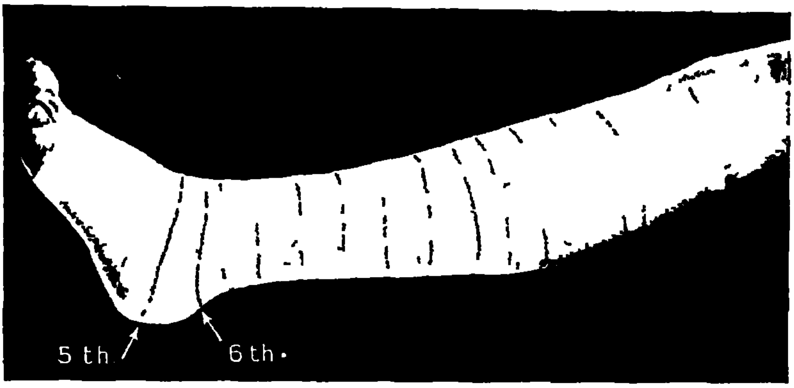

Fig. 2—Completed flexible adhesive outer bandage. Note method of circumnavigating ankle. The lower edge of the 5th turn is at the point of the heel, and the lower edge of the 6th at the insertion of the tendo Achillis.

Removal and Renewal

The first bandage should remain on for one week only, for this is the one that removes most of the œdema, and at the end of seven days it may be demonstrably looser than when first applied. For its removal we use special shears (Rivlin 1958), manufactured to our design by the Scholl Manufacturing Company. It is best to insert the shears under the bandage at the lateral border of the foot and cut along to reach the hollow behind the lateral malleolus, then cut up the lateral border of the leg along the muscular peroneal cushion, lifting the bandage off the skin as one cuts.

At the first removal we should see a leg virtually free of œdema, whose ulcer, if not smaller in area, is certainly more healthy-looking than a week previously, with a faint purple growing edge to its circumferential epithelium and early granulations within the formerly barren ulcer wastes. Continuation bandages should be applied as before until the ulcer is healed, remembering that the need now is probably not to squeeze out œdema but merely to hold the leg at its proper size. It is quite easy to overbandage legs, producing a thin pipe-like limb whose arterial inflow is undoubtedly disturbed. Unless patients are going on holiday, we make it a strict rule not to leave bandages on for more than a fortnight, otherwise autolysis from the ulcer discharge may cause local skin deterioration.

Results

In considering the immediate results of treatment three questions need answers:

1. How do the patients aged 60 and over compare with the younger ones?
2. Is there any outstanding difference in the speed of healing between the three groups of leg ulcers?
3. How rapidly can an ulcer be expected to heal?

On analysing the largest group, namely the *varicose* ulcers, we found that the average time of healing amounted to 10·2 weeks. The time averaged 11·5 weeks in those aged 60 and over and 9 weeks in the others (see table). But the average area of the ulcers when treatment was begun was over three times greater in the older than in the younger patients, and the rate of healing, expressed in square centimetres per fortnight, was three times greater in the elderly patients (see table). This accords with the suggestion that œdema causes gravitational ulceration, for, according to the clinical notes, œdema was far more pronounced in the older group—probably because the older patient has more opportunity and inclination to "rest". But, as soon as the œdema is banished, the ulcers heal as fast as in younger people.

RESULTS OF TREATMENT

Type of ulcer	Varicose			Post-thrombotic			Miscellaneous		
Age-group	20–59	60–90	All ages	20–59	60–90	All ages	20–59	60–90	All ages
No. of cases	77	73	150	22	8	30	9	11	20
Average healing-time (weeks)	9·0	11·5	10·2	11·2	15·0	12·8	10	16	13
Average size of ulcer (sq. cm.)	6·4	22·8	14·1	3·8	30·0	13·5	10	35	23·5
Average rate of healing (sq. cm. per fortnight)	1·2	3·6	2·6	0·7	4·0	2·1	2	5	4

In the case of the *post-thrombotic* and *miscellaneous* ulcers (see table), the ulcers in the older group remained under treatment longer, but again only because they were far larger to begin with. *Varicose* ulcers heal fastest of all.

Prevention of Recurrence

Briefly, the only ulcers that can really be cured are the varicose ulcers, but fortunately they form by far the largest group. A planned operation will rid these patients of their varicose veins, their tendency to gravitational œdema, and hence their ulceration. They need wear no form of support on their legs, can tear up their list of rules, and can behave as completely normal persons. Those who either do not wish to have an operation, or cannot have one, must be treated as the post-thrombotic group.

Ulcers of the post-thrombotic and miscellaneous groups cannot at present be fully cured although, of course, they can easily be healed, but an intelligent patient who understands the principles of œdema-prevention can keep his ulcer at bay without interfering very much with his normal life. He must keep faithfully to the rules, and *always* sleep with the foot of the bed raised 9 in. He should wear an elastic support on his legs. Neither elastic stockings nor the usual bandages are entirely satisfactory, but Messrs. Lastonet have produced a 5 in. × 7½ yd. (fully stretched) thin elastic net all-way stretch bandage† which moulds itself beautifully to the contours of the limb, is neither heavy, bulky, nor unsightly, and can be used for many months with frequent washing. Patients in the miscellaneous group must pay special attention to the re-education of the calf muscles.

Summary

The standard method of treatment at the London Varicose Clinic is described. Special importance is attached to the initial history and examination of the patient in order to classify the type of ulcer present as varicose, post-thrombotic, or miscellaneous.

Ambulation in proper footwear is by far the most important factor in treatment. Adhesive compression bandaging, using non-irritating materials, is ancillary to this but speeds up the rate of healing. Varicose ulcers can be expected to heal in ten weeks, post-thrombotic and miscellaneous ulcers in thirteen weeks. Instructions for applying bandages are given.

In the 200 consecutive cases of gravitational ulcer studied, elderly patients responded as rapidly to treatment as the younger ones.

True varicose ulcers can be cured by operation on the veins after the ulcer is healed. Post-thrombotic and miscellaneous ulcers can be kept at bay if the patient observes the principles of œdema prevention and venous return A new type of wide and light all-way-stretch supporting bandage is useful in the permanent aftercare of the post-thrombotic case

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† Now available on form E.C. 10.

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BLOOD-PRESSURE UNDER ANÆSTHESIA IN THE SITTING POSITION

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ONE of the main causes of brain damage or delayed recovery following dental anæsthesia may be its administration in the sitting position, according to Bourne (1957), who maintains that the blood-pressure may fall while nitrous oxide is being given, and that this indicates that the continued use of the sitting position for dental operations is unwise and likely to lead to permanent cerebral damage

Since the publication of Bourne's article we have recorded the blood-pressure of 100 unselected patients presenting unpremedicated at the Eastman Dental Hospital Their ages ranged from 5 to 65 years, and a breakdown of the cases into 5-year age-groups is shown in fig 1

Method

The blood-pressure was taken immediately after seating the patient in the chair and fixing the apron round his chest In each case the anæsthetic was administered by one of us, by a medical or a dental graduate, or by a medical undergraduate under supervision, with little or no variation in the results obtained by individual anæsthetists The operations lasted from one to eighteen minutes (fig 2) In the position adopted the patient sat with the seat of the chair tilting backwards but with the back-rest upright and the head-rest immediately under the occiput, so that he was in the "sniffing the morning air" position This is the position recommended for ease in nasal breathing

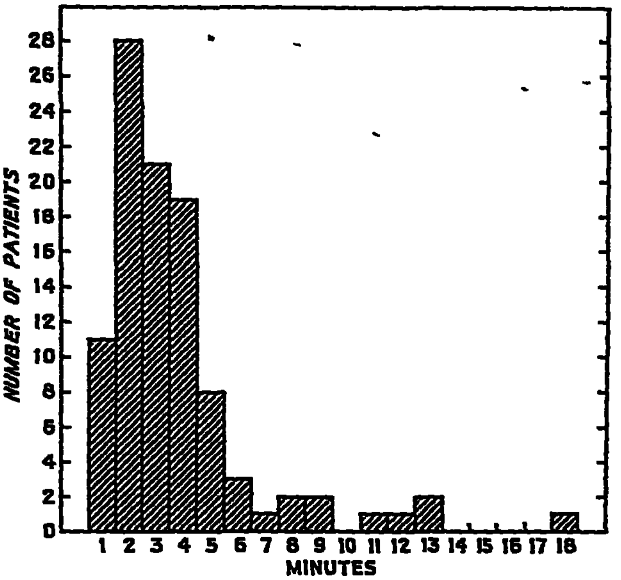

Fig 2—Duration of dental operation in 100 cases under general anæsthesia in the sitting position

The blood-pressure was taken at short intervals throughout the period of anæsthesia, five minutes after the patient had been removed from the dental chair to the recovery room in a wheel-chair, and again before the patient was allowed to leave the recovery room In all the cases the technique of induction was identical with that used and taught in this hospital for many years, and except in special cases, induction was with pure nitrous oxide until respiration became automatic, with inspiration shorter than expiration. At this point oxygen was administered to the patient, starting usually at about 8% and gradually increasing during the operation At the end of two minutes' operating the percentage of oxygen was usually increased to about 10%, and thenceforth by 1% at intervals of about a minute, even without any signs of anoxia During the whole operation an adequate and effective mouth pack was kept in situ to prevent both the inhalation of foreign bodies and dilution with air

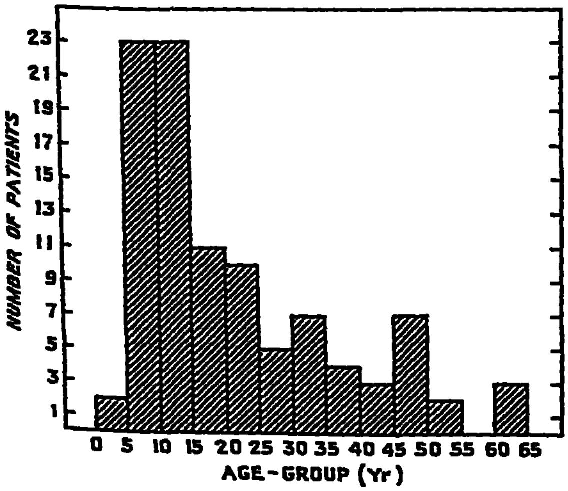

Fig 1—Age-distribution of 100 patients submitted to dental operations under general anæsthesia in the sitting position

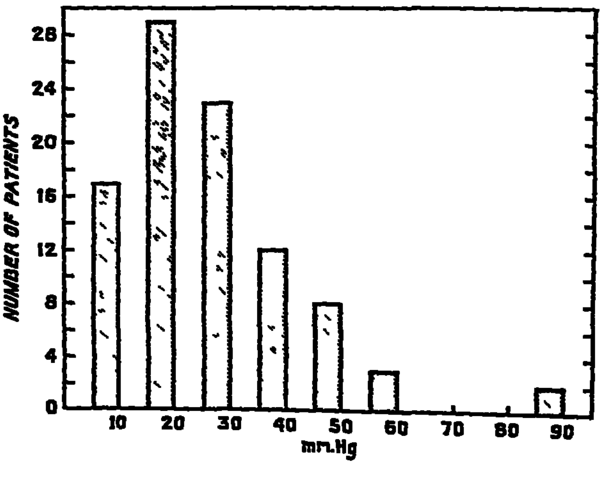

Fig 3—Amount of rise in systolic blood-pressure in 94 cases during administration of general anæsthetic with patient in the sitting position for dental operation

With this method of anæsthesia it was usual, at the end of five minutes' operating, for the patient to be receiving 12–14% of oxygen. If more extensive oral surgery was necessary and operating continued for more than ten minutes, the patient usually received 15%, 16%, or even 17% of oxygen with nitrous oxide. A rebreathing bag was not used unless the fractional rebreather on the McKesson machine was available, but in all the present cases no rebreathing bag was used, and consequently there was no retention of carbon dioxide.

The machines used were all tested on numerous occasions and gave oxygen percentages, under all conditions, within 1% of the amount indicated on the dial.

Results

In practically every case there was a rise above the initial blood-pressure. At the end of the period of anæsthesia, however, the blood-pressure fell, usually 5–10 m m Hg below the preoperative level, which might have been slightly raised through apprehension. It is, of course, impossible in these circumstances to get a blood-pressure reading under normal conditions without any stress or strain. However, in 94 cases systolic blood-pressure rose, at some point during the administration of the anæsthetic, above the preoperative and postoperative levels. The amounts of these rises are shown in fig 3.

21 of these patients had an initial rise of blood-pressure followed by a fall on the introduction of oxygen. In some cases the blood-pressure rose again, but at no time during the anæsthesia was the level lower than the postoperative reading.

In 9 cases there was an initial fall in blood-pressure after the start of the anæsthesia, but this level was not below the postoperative reading and was followed by a rise. These patients were usually excitable or very nervous.

In the remaining 64 cases there was an initial rise which was maintained throughout the period of anæsthesia.

In 6 cases the level of blood-pressure during anæsthesia was maintained steadily at the preoperative value, but the postoperative level in all cases was below this. The series included a child with a patent ductus arteriosus and a patient with a history of epilepsy. No delayed recovery or unusual effects were observed.

Discussion

It can therefore be assumed that the frequency with which syncope or fainting takes place under simple gas-oxygen anæsthesia is insufficient to cause great alarm, otherwise at least 1 case would have appeared in the present series, which included several lengthy operations.

This is a comforting thought because it confirms the safety of the practice of a hundred years' use of the sitting position, which in experienced hands does not increase the patient's risk of postoperative sequelæ. It is generally considered that the sitting position is the safest for dental operations in the absence of an endotracheal tube.

If, however, the sitting position had been shown to tend to produce complications, it would be necessary to operate on every patient supine. This would create a grave difficulty because, if more than four teeth were to be removed at one sitting, an endotracheal tube would be indicated in every case. Since about two million dental anæsthetics are given each year in the United Kingdom alone, this would mean a very great increase in the amount of work for hospitals and anæsthetists.

We hope that the result of our investigations will be accepted as proof that no special risk attends the routine that has been used for so many years, provided that nitrous oxide and oxygen are the sole anæsthetic agents used.

Summary

In 100 cases of dental extraction under nitrous oxide/oxygen anæsthesia there was an initial rise in blood-pressure above the preanæsthetic reading. This was usually maintained, but in some cases it fell with the introduction of oxygen, only to rise again to a level which was maintained to the end of the operation.

The blood-pressure fell to its preanæsthetic level or below within four minutes of the end of the administration of the anæsthetic agent.

No delayed recovery or untoward effects were observed.

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OTALGIA WITH ŒSOPHAGEAL HIATUS HERNIA

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SINCE 1956 we have seen three patients with a combination of earache and abdominal symptoms.

Case-reports

Case 1.—A woman, aged 55, was admitted with epigastric discomfort immediately after meals—in no way related to the type of food—and occasional heartburn. Elsewhere she had been found to have a large stone in the gallbladder, and this was suggested as the cause of her symptoms. But, as she gave no history of colicky pains, and as on cholecystography the gallbladder concentrated the dye well, one hesitated to ascribe all her complaints to the solitary gallstone.

When a more detailed history was taken, she mentioned that for years she had had a painful, itchy sensation in the right ear. Sometimes this became intolerable, and could not be relieved by scratching the external auditory meatus. She had been examined by various ear, nose and throat (E N T) specialists, but no abnormality could be detected. After one such examination she had been given a prescription for bromide "for the nerves". When questioned further about her abdominal complaints, she gave the following significant answer: "I always have the sensation at mealtimes as if food sticks just here," and pointed to the lower sternum. "It is as if a bubble of air sticks here and troubles me. It then suddenly shoots through, giving immediate relief."

This aroused suspicion of an œsophageal hiatus hernia. Although the pain in the right ear was the chief complaint, the patient had mentioned this hesitantly because she thought it was completely unrelated to the abdominal symptoms for which she had been referred to the surgeon. Yet the ear symptoms can be logically explained by the presence of hiatus hernia. Although this combination of symptoms is not common, it is mentioned in the French literature. The stomach was therefore re-examined radiographically, but a hiatus hernia was not demonstrable in Trendelenburg position.

Cholecystectomy was decided upon. At laparotomy the presence of a solitary gallstone was confirmed, but the gallbladder appeared otherwise normal. The œsophageal hiatus, however, admitted four fingers with ease, and the cardiac end of the stomach could be made to slide up through the hiatus.

The hiatus was then narrowed by approximation of the crura posterior to the œsophagus until it admitted only one finger next to the œsophagus. Cholecystectomy was then performed. Finally the operative correction of the hiatus hernia was completed by gastropexy to the anterior abdominal wall (Boerema and Germs 1955, Boerema 1958).

For obvious reasons, we had refrained from telling the patient before operation that there could be a connection between the earache and the abdominal complaints. Immediately after operation she spontaneously volunteered that the pain in her ear had disappeared. She was much gratified, but rather surprised that the earache had disappeared after an operation through the abdomen! A year later she is symptom-free. The otalgia has not recurred.

Now on the alert for the presence of ear symptoms with hiatus hernia, we found two further cases

Case 2.—A rather obese woman, aged 75, was admitted with upper abdominal complaints of at least 30 years' standing She had burning pain in the epigastrium and behind the lower sternum after meals This radiated through to the back between the shoulder-blades She often had severe heartburn. All the symptoms were aggravated by lying down after meals On bending forwards she had regurgitation of acid food into the mouth With swallowing, food seemed to lodge behind the lower sternum, she had to "swallow twice" to get it down

For years she had had an unpleasant painful itching in the left ear This came on simultaneously with the pain behind the lower sternum.

On radiological examination of the œsophagus and stomach, a large "sliding" hiatus hernia was demonstrated, and, as she had been treated conservatively elsewhere without success, we decided to repair the hernia surgically At laparotomy the stomach was reduced into the abdomen. The hiatus was narrowed by approximation of the diaphragmatic crura behind the œsophagus, after which an anterior gastropexy was performed

Six months later she was symptom-free, having had no further pain in the ear

Case 3.—A very obese woman, aged 71, had had cholecystectomy elsewhere 18 months before She was well till about 10 months after the operation when she developed upper abdominal discomfort after meals, which was relieved only by vomiting The symptoms were aggravated by bending forwards, but not by lying down.

For some months she had also had an irritation in the throat, a sensation as if there was a "lump" in the throat which she could not swallow down At mealtimes, however, she had no difficulty in swallowing food. Associated with this discomfort in the throat, she had a painful, itchy sensation in the left ear She had been referred to an E.N.T. surgeon, who could find no abnormality in the ears, pharynx or larynx, and she had been reassured and given vitamin-B tablets

On radiography of the œsophagus and stomach, a large "sliding" hiatus hernia was found. which did not reduce in the erect position At least a third of the stomach was in the chest

She was put on a reducing diet with frequent small meals, and slept in an upright position. On this regime the abdominal discomfort diminished significantly, and the earache disappeared. With such marked improvement of the complaints we found operation on this elderly, obese woman not indicated for the present She was therefore discharged with instructions to follow the above regime

Discussion

Many workers have mentioned that the epigastric or substernal pain of œsophageal hiatus hernia may radiate through to the back, down the arms, or up to the base of the neck, and sometimes even to the mouth or to the angles of the jaw In the French literature radiation to the ears is also mentioned Hillemand and Wattebled (1953), Hillemand et al. (1954) Dubost and Blondeau (1956) emphasise that the disturbances caused by hiatus hernia may appear completely unrelated to the gastrointestinal tract, with the result that patients are referred to specialists in other fields Hiatus hernia may for instance cause precordial symptoms which closely simulate angina pectoris An apparently causeless secondary anæmia may exist, the hernia being discovered only after careful examination of the gastrointestinal tract. Reflex vagal disturbances may lead to crises of bradycardia with a fall in blood-pressure and loss of consciousness

Hiatus hernia may also present with pain in the ears This may be the chief symptom, as described in the first case The mechanism of its production can be explained anatomically

The vagus nerve, after leaving the skull through the middle compartment of the jugular foramen, gives off an auricular branch This enters a small foramen on the lateral wall of the jugular fossa and traverses a special canal, the mastoid canaliculus, in the mastoid part of the temporal bone It then divides into two branches which are distributed to the external auditory meatus and to a small area of skin over the mastoid process (Spalteholz 1921)

The vagus then passes down into the neck giving off its pharyngeal, laryngeal, and cardiac branches In the thorax it forms the pulmonary plexus for the supply of the lungs and the œsophageal plexus The œsophagus is supplied proximally by branches directly from the vagal trunk and distally by the œsophageal plexus

Gray's Anatomy (1946) described various "reflexes" in connection with branches of the vagus The "ear cough" is mentioned as one of the commonest. A plug of wax in the external auditory meatus may, by irritating the filaments of the auricular branch, be responsible for a persistent cough Syringing the auditory meatus may similarly produce coughing, or, in children, vomiting, moreover, syringing the ear has been responsible for a sudden fatal syncope, by reflex irritation of the cardiac branches Another common example quoted is the persistent cough which is common with enlarged bronchial lymph-glands in children, the irritation is referred to the superior laryngeal filaments

Reflexes in connection with the vagus and its auricular branch are therefore not uncommon. Similarly the phenomenon of otalgia with hiatus hernia can be explained as a referred pain along these vagus pathways Irritation of the œsophageal filaments produces stimuli which are centrally misinterpreted as coming from the auricular branch. Thus a painful itching in the ear results The vagus or its œsophageal branches may be irritated by pressure on the nerve in the hiatus, by stretching of the nerve over the hernial mass in the case of a large hernia or by periœsophageal inflammation where the hiatal hernia is complicated by œsophagitis

In the two cases where the hiatus hernia was surgically repaired the earache disappeared immediately after operation The irritation of the vagus nerve was therefore probably caused by a stretching or compression of the nerve by the hernia

Patients with a persistent, painful, itchy sensation in the external auditory meatus for which no local explanation can be found, and who may or may not have associated upper abdominal or substernal complaints, should therefore be examined for the presence of œsophageal hiatus hernia

Summary

Three cases are described in which œsophageal hiatus hernia was associated with pain in the ear The anatomical basis for this phenomenon is that both œsophagus and external auditory meatus are supplied by the vagus nerve, and the pain is probably referred The earache disappeared after effective treatment of the hernia

I wish to thank Prof I Boerema, head of the department of surgery, for encouragement and permission to publish these cases

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CORTISONE IN THE TREATMENT OF ACUTE MILIARY TUBERCULOSIS

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> " Surely every medicine is an innovation and he that will not apply new remedies must expect new evils "
>
> FRANCIS BACON

YESTERDAY cortisone was considered to be contraindicated in tuberculosis, today considerable trials are being conducted using steroids in tuberculosis therapy The case presented is one thus treated

Case-report

A man, aged 64, had worked in an iron foundry for 36 years and latterly had been subject to mild bronchitis 4 years ago he retired from the foundry and took to " odd-jobbing " Just before Christmas, 1956, he worked 1 day in a local cotton-mill and then developed a " bad chest ", with left pleuritic pain and a cough He became feverish and was losing weight rapidly By Feb 7 he had taken to his bed, finally not eating or drinking and becoming confused

He attended the geriatric outpatient clinic on Feb 21, 1957, complaining of left chest pain, dyspnœa, cough, loss of appetite and of weight, sweating, and occasional vomiting He was somewhat confused and appeared very ill indeed He coughed day and night, with half a cup of yellow sputum a day, no hæmoptysis He was pale and wasted, temperature 100 4°F, pulse-rate (regular) 142 a minute, respiration-rate 28 a minute

His trachea was central, chest expansion fair and symmetrical, percussion-note resonant with slight impairment at the left base, and breath sounds vesicular with numerous medium rales, especially left base No abnormalities were found in other systems, apart from dulled level of consciousness

A provisional diagnosis was made of unresolved pneumonia with effusion or empyema, he was admitted His hæmoglobin was 64%, leucocyte-count 6400 per c mm, erythrocyte-sedimentation rate (E S R) 34 mm in the first hour He appeared to be dying and was considered unfit for X-ray screening Aureomycin was given

Over the next 5 days there was no change, the pyrexia continued The chest remained surprisingly quiet, with fewer moist sounds at bases than on admission The impairment at the left base had disappeared and a diagnostic pleurocentesis was not performed Sputum gave growth of normal flora Electrocardiogram normal A radiograph of the chest showed " extensive miliary mottling in all zones of both lung fields Appearances of miliary tuberculosis or pneumoconiosis " Examination of eyes showed a tubercle in the lower right conjunctival sac and two patches identical with miliary tubercle in the right fundus

Mantoux 1/10,000 was negative The cerebrospinal fluid (C S F) was opalescent, pressure 135 mm Protein 80 mg per 100 ml, globulin slight increase, Lange 1111100000, chlorides 565 mg per 100 ml, sugar less than 20 mg, cells 36 per c mm (polymorphs 50%, lymphocytes 50%) No organisms Wassermann reaction negative Culture yielded no growth Streptomycin 1 g b d and isoniazid 100 mg t d s started

On March 2 the Mantoux test was still negative After some slight initial improvement, the patient again appeared to be dying The dose of isoniazid was increased to 100 mg 6-hourly and cortisone acetate 25 mg q d s was begun At this stage his weight was 8 stone

After a few days he began taking some food and his condition improved slowly, but later more rapidly Streptomycin was reduced to 0 5 g b d The C S F contained protein 44 mg per 100 ml, sugar 49 mg, cells 72 per c mm (polymorphs 40%, lymphocytes 60%) Guineapig inoculation was negative

5 weeks after admission weight 9 stone On the chest radiograph, " miliary nodulation, though still extensive, appears less accentuated " E S R 50 mm in the first hour

By April 14 he was very much better The cortisone had been gradually discontinued Mantoux 1/10,000 became positive 24-hour specimens of urine and sputum throughout yielded no acid-fast bacilli The E S R remained raised

On June 6, the chest radiograph showed " very marked improvement, especially compared with original films Still faint reticulation and residual fibrosis at both bases " Later in June his weight was 10 stone, his E S R fell, and he was allowed home but continuing therapy The streptomycin and isoniazid were finally discontinued in August

In September the chest radiograph continued " to show improvement with some residual fibrosis " He is still under outpatient observation and remains very well

Discussion

This man, originally Mantoux-negative, had had mild chronic bronchitis for years after a lifetime in an iron foundry There is, therefore, the possibility of some degree of pneumoconiosis, and this is supported by the chest radiographs The later films show a fine reticulation which could be a reaction to dust or a streptomycin-treated-tuberculosis pattern He gave a vague history of having had " pneumonia " several times in 1950, but was treated at home and never radiographed

Although acid-fast bacilli were never isolated from his sputum, urine, or C S F, the response to streptomycin and isoniazid, together with the radiological picture of his chest, justify a diagnosis of miliary tuberculosis The fact that his Mantoux later became positive is also evidence in favour of such a diagnosis, though tuberculin sensitivity is occasionally depressed in acute stages of the illness The diagnosis of pneumoconiosis alone is excluded by the clinical picture and the final response to the therapeutic measures taken Until recent years acute miliary tuberculosis was considered a disease of young people, but more cases are now being reported in older ones

There were no physical signs of meningitis, except the abnormalities in the C S F, hence intrathecal therapy was not given, in the belief that isoniazid, given orally, freely enters the C S F, and that this would be sufficient in this particular case

Because of the ability of cortisone to alter fibrinogenesis and thus prevent the formation of adhesions, it is being used in tuberculous meningitis in many centres (Shane and Reilly 1953, Ashby and Grant 1955) Wasz-Höckert (1954) describes corticosteroids as " routine " in the treatment of tuberculous meningitis in Helsinki Choremis et al (1957) have used similar treatment in children All believe that cortisone has a definite beneficial effect on the clinical course and final result

When cortisone is used, the appropriate antimicrobial therapy must be given It is most useful in overwhelming toxic states, where immediate improvement of the patient's condition is imperative Cortisone does not interfere with phagocytosis, but deprives the monocytes of much of their capacity to inhibit the intracellular accumulation of bacilli (Lurie 1957) The result, therefore, is more primary tubercles, which are small and incompletely caseous, swarming with bacilli, with very little interstitial reaction

Lurie has pointed out that cortisone, by virtue of its anti-inflammatory effect, greatly hinders lymphogenous and hæmatogenous dissemination of bacilli When tuberculosis spreads under the influence of cortisone it does so by contiguity, with the movement of tuberculous macrophages

Shmelev (1957) has shown that cortisone given in the initial stages of disseminated tuberculosis can decrease the number and size of foci, reducing the exudative reaction, and that using cortisone with antituberculous drugs gives a better therapeutic effect than using antituberculous drugs alone

McLeod Riggins (1957) says that cortisone in tuberculosis has a threefold effect (1) anti-inflammatory (whether useful or not?), (2) anti-allergic (partial suppression of the hypersensitive state, which may be useful in various forms of acute tuberculosis), and (3) therapeutic, especially if tuberculosis is complicated by adrenocortical insufficiency In this case cortisone was administered initially for the last effect—as a " tonic " The patient appeared to be dying and it was felt cortisone might just turn the scale

Pharmacological, and not toxic, doses must be used, for the danger of hypercorticism is real, and the suppression of adrenocortical function, when cortisone is stopped after a long course, may not only produce addisonian symptoms but also reduce resistance to infection

Chenebault (1957) reported a series of 117 varied cases of tuberculosis which he treated with cortisone or allied steroids Spectacular results were seen in the miliary cases in 5 to 6 weeks Moribund patients became convalescent in 6 weeks Radiological improvement was "extraordinary", with an equally rapid general transformation

In conclusion, as always when spectacular results are reported, caution is very necessary As Kaufmann (1957) says, cortisone treatment is indicated particularly in patients with a toxic course and in those with a tendency to excessive mesenchymal defence reaction A careful selection of patients is indispensable

Summary

A man of 64 appeared moribund from miliary tuberculosis When given cortisone (in conjunction with streptomycin and isoniazid) he improved strikingly, and later he was discharged fit

Cortisone is indicated in selected cases of tuberculosis, where the course is toxic or the mesenchymal reaction excessive Antituberculous drugs must be given as well

I am grateful to Dr W H Lloyd, consultant geriatrician, for permission to publish this case and for the encouragement he has given me throughout I also want to thank Dr D Plowman and Dr T D O'Brien (registrars in the geriatric unit), Dr D A H Walton, Dr E Ratner, Dr C H Adderley, and Dr L B Hardman

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New Inventions

BED WITH BEDPAN

THE bedpan, as ordinarily used, has many disadvantages, and patients have expressed approval of a bed which I have designed to overcome some of the objections

A standard type of hospital bed is modified so that part of the frame containing the mattress is extensible (fig 1) Beneath the mattress, resting in a light metal frame, is a movable tray which can be raised to the level of the mattress by means of two arms on either side The tray contains the bedpan, which can be easily inserted or removed by means of a movable handle when not in use, this is flush with the surface of the tray When the bedpan is needed, the slots at the foot of the bed are opened, and this allows the movable part of the frame to be extended When it has been extended enough to clear the underlying tray (fig 2), the screw on the side of the movable part of the frame is tightened to prevent further extension The tray containing the bedpan is then raised into position so that it comes to rest at the level of the top of the mattress (fig 3) and the patient can now slide on to the seat

If necessary, the locking screw may be released and the bed further extended to allow the patient's feet to come down to the floor, enabling him to assume the correct position for defæcation When the pan has been used the legs are raised by nurses and placed on the mattress The screw is released and the frame partially closed, the screw is then tightened and the patient slides back on to the bed

A lid is applied to the receptacle, which is lifted out of the tray, the tray is then lowered The lock holding the movable part of the frame in position is then released, the bed is closed, and finally the slots at the foot of the bed are shut Nurses have found the bed easy to work, but in the prototype the tray has proved rather heavy Further improvements suggested are a lighter tray, made from aluminium and covered with 'Formica' or polyethylene, and a plastic receptacle, which should have a spout anteriorly instead of being circular

A standard hospital bed of this type has been modified by Messrs James Sherret and Sons, Brechin

Stracathro Hospital,
Brechin, Angus

J REAY ARMSTRONG
M A , M D Cantab

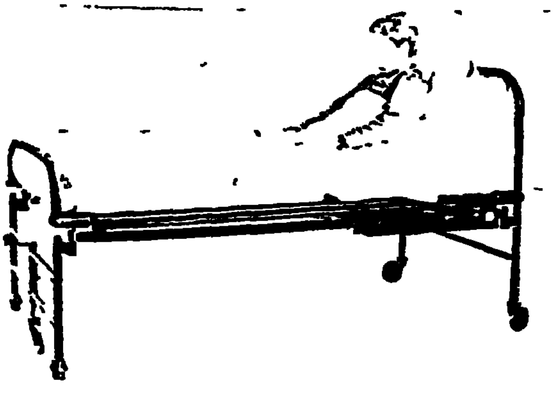

Fig 1—Bed in ordinary position, closed

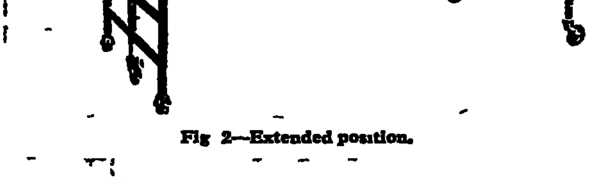

Fig 2—Extended position.

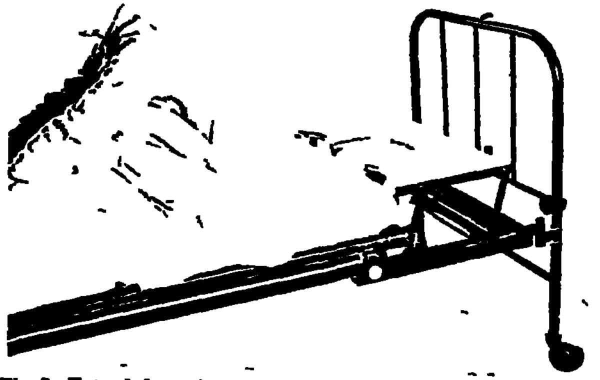

Fig 3—Extended position with tray containing bedpan elevated and ready for use

Reviews of Books

Australia in the War of 1939–1945

Medical Series The Island Campaigns ALLAN S WALKER, M D, CH M, F R A C P Canberra Australian War Memorial London Angus & Robertson 1958 Pp 426 35*s*

OUR soldiers in Burma talked of themselves as "forgotten men", but some of them who heard the late Brigadier J A Sinton, V C, on the Australian conquest of malaria realised at the time how little they knew of the even less publicised war in New Guinea and the near-by islands The conditions, climatic and geographical, were not unlike those in northern Burma heavy rainfall, flooded rivers, lack of roads—and malaria No-one has yet written a connected account of the work done by Sir Neil Hamilton Fairley and his associates on experimental malaria and the applications of their results to an army fighting a mobile war in an area where malaria is hyperendemic Public imagination was stirred by the patient and inconspicuous work which gave us better weapons of war, but if ever a war was won "out of sight" it was at Cairns Since then the methods have been improved, and in peace it is generally true that it is poverty rather than ignorance which allows malaria to survive This book has much to say of Fairley's work in the laboratory and in the field, but because it is a chronological account of the medical services in campaigns often fought simultaneously the account is disconnected

Because of the similarity in conditions, the book will be of most interest to those who fought in Burma, but there were some obvious differences Air support and supply seem to have been on a smaller scale in the islands, but far more use could be made of the sea the natives were more numerous and usually friendly and helpful the numbers engaged were less and there was no big battle comparable with the crossing of the Irrawaddy Both were junior officers' wars in which success and failure were obvious to everyone In both there was general agreement on the main problems of military medicine forward surgery followed by quick evacuation of the wounded, the malarious to be held near the line until fit for duty, preventive medicine not the responsibility of the "sanitary squad" but of every man in every rank

This is a very interesting book but not an easy one to read It seems that every medical participant is mentioned by name, each stage of evacuation is detailed at every point, and every move of each field ambulance is marked on the map For those who fought elsewhere the book would be better for wider survey of the campaign Pictures and maps are abundant and to the point

Diseases of the External Ear

BEN H SENTURIA, M D, associate professor of clinical otolaryngology, Washington University School of Medicine Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1957 Pp 211 63*s*

DISEASES of the skin of the external auditory meatus are hard to treat The otologist is well qualified to examine the ear canal but his training in dermatology is often insufficient to differentiate the various manifestations of skin disease there The dermatologist, on the other hand, is usually not equipped to examine and apply treatment to the external meatus Otitis externa has thus been relegated to a therapeutic no-man's-land with little basic research to aid those striving after logical treatment based on pathological and ætiological facts

Dr Senturia and the ten colleagues who helped him have done a great deal to fill the gaps by drawing on their large experience of civilian and Service patients In a well-documented monograph the many ætiological factors are discussed and the various lesions of the external canal described In a series of animal experiments otitis externa was reproduced by means of bacterial contamination combined with trauma and/or lipid removal Among the most important causes is the loss of the protective layer of waxy sebaceous secretions in times of stress, during swimming, &c The section on treatment includes advice on preventive protection of the meatal skin by wax-like ointments The book goes a long way to formulate a rational approach to this troublesome condition

Neuritis, Sensory Neuritis, Neuralgia

R WARTENBERG, M D New York and London Oxford University Press 1958 Pp 444 68*s*

BASED on his own experience and illustrated by a number of case-records, this book was completed by Dr Wartenberg shortly before his death in 1956 It emphasises the importance of mononeuritis—neuritis of a single peripheral nerve—either solitary or in association with neuritis of other peripheral nerves It does not deal, except for the sake of contrast, with polyneuritis of the Guillain-Barré and allied types The book contains a substantial bibliography (the author's assurance that he has actually consulted the items he refers to may startle some readers)

One of his main purposes is to demonstrate that a mononeuritis may result from a general systemic affection and to emphasise the clinical importance of isolated infectious mononeuritis It is stimulating to read the vigorous attack on prolapsed intervertebral disc as a cause of sciatica and to consider the rival claims of sciatic neuritis, but many will think that in this as in other directions the claims of "neuritis" are pushed too hard, especially since the diagnosis is purely clinical and unsupported by any pathological evidence

Biographical Memoirs of Fellows of the Royal Society

Vol 3 London The Royal Society 1957 Pp 328 30*s*

THIS volume contains twenty-one notable biographies, each preceded by a portrait, often of unusual excellence (one of a botanist is appropriately in colour) About a third have important medical interests Arthur Felix was one of the unique personalities of medical bacteriology, who will be remembered for his work in connection with the Weil-Felix reaction and for his discovery of the H and O antigens of organisms of the proteus and enteric groups Percival Hartley's outstanding services were concentrated on therapeutic science and biological standards Albert Jan Kluyver left a record of service to microbiology that will be hard to equal Henry Nicholas Ridley, a botanist, published papers of medical interest including one on Chinese anti-opium drugs Frederick Soddy, a chemist, was awarded a Nobel prize for his part in the conception of isotopes John William Trevan, the research director of the Wellcome Foundation, did important work in pharmacology, he once said modestly that he had had the satisfaction of starting a number of hares, most of which had finally been caught by others Hubert Maitland Turnbull had an influence in pathology far beyond the London Hospital, he had a genius for accuracy of observation and meticulous attention to detail, which he applied with fervour to everything he did Other biographies concern astronomers and mathematicians and are illustrated with rows of forbidding formulæ and equations

This splendid book should enter all scientific libraries and *all the major medical ones*

Preventive Medicine for the Doctor in his Community (*An Epidemologic Approach* 2nd ed New York and London McGraw-Hill 1958 Pp 689 77*s* 6*d*)—The first edition of this book by Prof H R Leavell, of Harvard, and Prof E Gurney Clark, of Columbia University, appeared in 1953[1] The new one is 60 pages longer, chiefly because a chapter on oral disease has been included The title has been altered from *Textbook of Preventive Medicine* and now indicates that the book is aimed at the student and practising doctor and not the specialist in preventive medicine, although there is much that the specialist can learn from it The arrangement has also been changed and the chapters are grouped into Basic Principles, Application of Principles, and Public Health—Preventive Medicine as Organised Community Action The book is unique in its field

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[1] *Lancet*, 1953, ii, 170

THE LANCET
LONDON 28 JUNE 1958

Surgery for Pulmonary Tuberculosis

THE research committee of the British Tuberculosis Association began in 1952 to plan a comprehensive survey of the results of major surgical treatment of pulmonary tuberculosis They were joined by the Society of Thoracic Surgeons of Great Britain and Ireland and aided financially by the Medical Research Council The first report of this interesting joint enterprise has just been published.[1]

Seventy-four thoracic surgeons in the United Kingdom provided information about patients operated on during a period of twelve months in 1953 and 1954 Reference to the theatre-lists of the cooperating hospitals showed that only 12 operations were not reported—a remarkable achievement. 8236 operations were recorded This was probably 1 operation for every two or three patients with infectious sputum during the period, which indicates the magnitude of the flood of surgical treatment that followed the discovery of effective chemotherapy 6050 patients had "active" disease limited to one lung without such preoperative complications as empyema or fistula 3100 underwent some collapse operation—all but 405 a thoracoplasty—and 2950 had the whole or part of the lung removed The report deals with the two-year follow-up of these 6050 patients Such a survey requires willing cooperation from a large number of people—surgeons, physicians, and registrars If the record form is too complex, the information put on it by the clinicians may be less complete and accurate than if only a few simple facts are required Those who planned the investigation rightly chose to sacrifice detail for the sake of comprehensiveness and accuracy, and it must have been difficult to decide what detail to omit. It is unfortunate that in one respect they seem to have chosen wrongly, for details of chemotherapy were so scantily recorded that, according to the report, no use could be made of them at all The supreme importance of the correct choice of drugs and dosage and of prolonged administration was, of course, far less widely known in 1952 than it is now

Because of this serious deficiency, the recorded results of surgical treatment can be used only for internal comparisons, and even here the observed differences must be interpreted cautiously, for it is not known whether the groups on the two sides of each comparison were comparable in respect of the most important prognostic factor—drug treatment Certainly the results cannot be translated into present-day practice without reserve For instance, as many as 20% of patients without cavitated lesions had had either no chemotherapy at all or less than six weeks' chemotherapy at any stage before operation Even among the 4773 with cavities 4% had had no chemotherapy, and 45% had had infectious bronchial secretions in the three months before operation The presence of drug-resistant strains in pretreatment cultures was not recorded, no doubt because drug-sensitivity tests were not being done as a routine in all centres—nor were they being performed by the same or comparable techniques Possibly this difficulty could not have been overcome, but it seems a pity that so much valuable information about the influence of chemotherapy on surgical results had to be left out of the survey

The investigation has nevertheless yielded many valuable findings Two years after operation 85% of the whole 6050 patients were fit for work and had no signs of "active" tuberculosis A further 4% had no "active" disease, but for various reasons were unfit for work. 6% still had "active" disease, and 3% had died during the period (2% were untraced) Of the 2695 who had a thoracoplasty 2 3% died within two years 1392 had a lobectomy and 2 9% died With segmental resection the mortality was only 1 4%, but with pneumonectomy it was 10 6% These figures should not, of course, be used to compare the efficacy of the various operations, for they were done for different types of lesions and on different categories of patients For instance, 51% of those with cavities had a thoracoplasty and only 41% a resection, while the corresponding proportions among those without cavities were 20% and 76% Collapse operations were more usual in the old than the young and less common in women than men The closest approximation to a valid comparison between resection and thoracoplasty for similar types of disease can be obtained from studying the patients with cavitated lesions confined to the upper lobe There were 3514 of these In general, the more favourable cases were chosen for resection Thus, fewer had infectious sputum, healed contralateral disease, a history of five years or more, and impaired pulmonary function Despite this, the two-year results were similar following resection 89% had no "active" tuberculosis and 2 8% had died, whereas after thoracoplasty 88% had no "active" tuberculosis and 2 3% had died Further analysis showed that thoracoplasty tended to produce slightly better results in the less favourable cases In patients with both contralateral disease and recently infectious sputum there were, after two years, 3% deaths and 86% with no "active" tuberculosis among those who had undergone thoracoplasty, compared with 6% and 83% among those who had undergone resection

As expected, bronchopleural fistula proved an important complication of surgical treatment A fistula developed in 5% of patients after resection, but in a little less than 1% after collapse (and 6 of the 19 fistulas in the thoracoplasty patients followed a later resection) Infected fistula with empyema was five times commoner with cavitated lesions than with non-cavitated lesions, and arose three times more commonly in patients with infectious sputum within the three months preceding operation than in others Fistula was commoner on the right than the left side. The prognosis with infected fistulas was poor, after two years, only 41% of patients in this category were fit and free from "active" tuberculosis, and 22% had died With better drug treatment and more discriminating choice of patients for surgical treatment, the risks of this grave complication should now be considerably smaller

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[1] Major Surgery for Pulmonary Tuberculosis By R S FRANCIS and M P CURWEN London Staples Press Pp 96 1955 12s 6d

One of the current problems in surgical treatment is whether to resect portions of lung containing non-cavitated tuberculous nodules in patients who have been treated by long and effective drug regimes and whose sputum, gastric contents, and laryngeal swabs are not found to contain tubercle bacilli This survey certainly shows that such patients are likely to fare well after surgical treatment There were 843 treated by resection or collapse operations who had either never had positive results of sputum examinations or not had a positive result in the six months preceding operation By the end of two years 0 7% had died, 2 3% still had "active" tuberculosis, and 95% were free from "active" disease, almost all of these being fit for work (2% were untraced) The results can be expected to be better with more efficient chemotherapy But these figures cannot be validly used to provide a reason for surgical treatment in such cases, for there are no two-year follow-up results for comparable patients treated without operation The results without surgery may be as good or better Another problem is whether to treat surgically those patients with persisting cavities but no evidence that tubercle bacilli are being excreted in the bronchial secretions while chemotherapy is continued Here also the survey gives little help There were 1354 patients with cavities who had not had a positive sputum result for more than six months before operation After two years 2 1% were dead and 4 9% still had "active" disease, 91% had no "active" disease (2% were untraced) But we do not know what chemotherapy these patients had had before and after operation, nor do we yet know what happens to patients with persisting cavities treated by efficacious drug regimes Some facts have been established by examining resected specimens of lung after treatment of different durations[2], others are being obtained by following up patients who are not operated on But it is doubtful whether it is at present possible to establish a rational treatment of both these groups of patients Certainly no dogmatic statements of policy can be anything more than expressions of belief

Carefully controlled studies of the experiences of patients of different categories randomly allocated to surgical and non-surgical groups could give valuable information Possibly in 1952, when the British Tuberculosis Association survey was planned, the time was not ripe for such an investigation Surgical treatment was popular, and long-continued chemotherapy had been little used Possibly there would have been too few physicians and surgeons with sufficient belief in the efficacy of chemotherapy to provide adequate numbers of patients Even so, it is a pity that the attempt was not made, for it seems likely that the pendulum has now swung so far the other way that such an investigation would still be unacceptable—this time because too many clinicians might be unwilling to cooperate, having seen the apparently excellent results of sustained chemotherapy without surgical treatment Operations to prevent an unknown and probably small risk of relapse in the remote future do not generally commend themselves to physicians

This, despite its imperfections, is an important survey, showing how much can be achieved by large-scale cooperation among clinicians It has been said of the survey that it is "doubtful whether in any other disease it would have been possible to present such a comprehensive picture of the results of surgical treatment the patients being treated and observed in an administrative framework almost ideally suited to large scale clinical research of this nature"[3] Chest physicians and surgeons are well placed to carry out such work through their professional organisations the British Tuberculosis Association, the Tuberculosis Society of Scotland, the Thoracic Society, and the Society of Thoracic Surgeons Several useful cooperative investigations have been made in the past few years by the British Tuberculosis Association[4] and the Tuberculosis Society of Scotland[5], and the former is collaborating with the Royal College of Obstetricians and Gynæcologists in a study of endometrial tuberculosis[6] and with the Society of Thoracic Surgeons in the survey of major surgery in pulmonary tuberculosis Next week the Association will be discussing this report at its annual conference, to be held in London

Isotopes in Absorption Studies

ISOTOPE-LABELLED fats, proteins, and vitamins are being keenly used for the study of intestinal absorption, even though some have not proved as useful as was predicted In 1949 STANLEY and THANNHAUSER[7] noted increased radioactivity in the blood after the feeding of ^{131}I-labelled olive-oil Subsequently LAVIK[8] and CHINN[9] and their co-workers developed the use of ^{131}I-labelled protein as a test of pancreatic function, pointing out that the rise in plasma values depends on the ability of the pancreas to digest labelled protein and of the normal intestine to absorb at least 90% of the digested protein The validity of the technique rests on the assumption that the iodine tag remains firmly attached during the passage of the fat or aminoacid through the intestinal cell Both TURNER and DUFFY[10,11] and REEMTSMA et al[12] with improved techniques have presented evidence that this assumption is correct

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[3] Leading article *ibid* 1958 39, 183

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[5] *Brit med J* 1957, ii, 1131 *Tubercle Lond* 1957, 38, 375 *ibid* 1958, 39, 129

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[9] Chinn, A B Lavik P S, Stitt R M Buckaloo G W *New Engl J Med* 1952, 247, 877

[10] Turner, D A, PH D thesis, University of Ontario, London, Ontario, 1956

[11] Duffy B J, Turner D A *Ann intern Med* 1958 48 1

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Both groups used ^{131}I-labelled oleic acid and ^{131}I-labelled triolein in developing a specific test for pancreatic insufficiency The basis of the test is that triolein (a neutral fat) requires pancreatic lipase for its hydrolysis before absorption, and ^{131}I-labelled oleic acid (a fatty acid) can be absorbed normally in the absence of pancreatic lipase In diseases of the intestinal wall, absorption curves of both substances are depressed—for example, in adult cœliac disease, intestinal lipodystrophy, and regional ileitis A normal curve after the administration of either ^{131}I-labelled triolein or protein should effectively eliminate pancreatic insufficiency as a cause of diarrhœa In obstructive jaundice evidence of pancreatic insufficiency obtained in this way is usually associated with carcinoma of the pancreas [13] Neither ^{131}I-labelled triolein nor ^{131}I-labelled albumin is of use in detecting localised neoplasm in the body of the pancreas

Such a simple interpretation of the tests cannot be applied in cases of obstructive jaundice In one of the more detailed investigations KIRSNER et al [14] noted low curves in 2 patients with carcinoma of the common duct, in whom the pancreatic enzymes were normal and the pancreas and small intestine were normal at necropsy Moreover, in cases of high-grade pyloric stenosis the results can be anomalous, and the curves might be particularly misleading in those occasional patients who have pyloric stenosis and intermittent diarrhœa KIRSNER et al [14] found excellent correlation between the curves of a ^{131}I-labelled triolein and the amounts of fat actually excreted in the stools There was in addition good correlation between the proportion of radio-isotope absorbed and the degree of steatorrhœa, except in patients with regional ileitis It might perhaps be inferred that the correlation is somewhat fortuitous since improvement in the absorptive curves in adult cœliac disease, for example, may long precede decrease of steatorrhœa KIRSNER et al noted that the absorptive curves correlated closely with the vitamin-A curves, but they concluded that it was easier to measure radioactivity in the plasma than the vitamin-A level RUFFIN et al ,[15] who have had extensive experience with ^{131}I-labelled lipids, concluded that the tests were simple and reliable, accurately reflecting fat absorption If patients who had undergone gastric operations were excluded, there were no false positive results, but the tests might be normal in patients with organic intestinal disorders In 60% of patients who had undergone operation for peptic ulcer with or without vagotomy, they noted impaired absorption of triolein Such a finding signified either impaired digestion or impaired absorption, but since the levels following oleic acid were usually normal the abnormalities must be primarily of digestion rather than of absorption Nevertheless it must be admitted that labelled fats and proteins do not give any better results than chemical methods in the detection of absorptive defects [16] The correlation of fæcal fat with plasma curves or isotope fæcal excretion is not invariably close, and, in patients in whom the defect is slight, interpretation is difficult Indeed, it would be surprising if the absorptive curves of the isotopic material were completely reliable since they are open to the errors of interpretation common to any absorptive curve

If studies with isotopic oleic acid, triolein, and amino-acids have been disappointing, because of their inability to provide clear-cut answers in doubtful cases, vitamin B$_{12}$ labelled with ^{56}Co, ^{58}Co, or ^{60}Co has led to a great increase in the knowledge of the absorption of cyanocobalamin—knowledge which can be put to practical use [17–19] Three techniques have been used—measurement of the radioactivity in the fæces,[20] measurement of the hepatic uptake,[21] and measurement of the proportion excreted in the urine [22 23] When these techniques were applied to patients with intestinal disorders it soon became evident that lack of intrinsic factor was by no means the only cause of failure of absorption of vitamin B$_{12}$, and that different parts of the intestinal tract differed in their capacity to absorb the vitamin Furthermore, there is a limit to the amount of vitamin B$_{12}$ that can be absorbed from the gut [24] The optimum dosage of labelled vitamin B$_{12}$ falls within the physiological range for absorption of this vitamin (0 5–2 µg) [22] If extremely large doses of vitamin B$_{12}$ (500 µg or more) are administered by mouth or by rectum this limiting effect may be overcome by the " mass action " effect both in pernicious anæmia [25] and in primary malabsorption syndrome [26] CASTLE [27] suggested that vitamin B$_{12}$ was absorbed mainly high in the small intestine, and CITRIN et al ,[28] who instilled labelled vitamin B$_{12}$ into the upper and lower ileum, considered that in normal circumstances this was probably true But MCINTYRE and her colleagues [29] in 2 patients with about a foot of jejunum remaining, and MOLLIN et al [30] in 3 patients with three to four feet of jejunum, were unable to demonstrate any absorption of vitamin B$_{12}$ Evidence from intestinal resection suggests that vitamin B$_{12}$ is absorbed from the ileum, and even when only two to three feet of the terminal ileum are involved, as in regional ileitis, significant impairment of absorption may be demonstrated [26 29]

Studies on patients with idiopathic steatorrhœa have shown that a high proportion do not absorb vitamin B$_{12}$[21 26 30 31] and that absorption cannot be improved by the addition of intrinsic factor or antibiotics though it is by steroid therapy **MOLLIN** et al,[30] however, called attention to patients with steatorrhœa and with gastric atrophy of the addisonian type in whom vitamin B_{12} was absorbed in addition to the intrinsic factor Whether this atrophy can be considered specific is questionable,[32] and it may well be encountered in some patients with idiopathic steatorrhœa Another condition which can interfere with the normal absorption of vitamin B_{12} is that associated with intestinal diverticulosis[33] In such patients megaloblastic anæmia is liable to develop, owing to deficiency of vitamin B_{12}, this, it has been suggested, is due to over-growth in the diverticula of intestinal bacteria which utilise the available vitamin B_{12} The anæmia often responds to aureomycin (chlortetracycline),[30] but not to neomycin[34], occasionally it responds to the addition of intrinsic factor[31] **MOLLIN** et al[30] found normal absorption of vitamin B_{12} in pancreatic steatorrhœa, while **MCINTYRE** et al[29] found in 4 patients impaired absorption, which was not improved by intrinsic factor, antibiotics, or pancreatin, but a 5th patient, who had all her pancreas removed, absorbed vitamin B_{12} normally, so it must be concluded that deficiency of pancreatin secretions could not have been the operative factor in their previous 4 patients Thus, while radioactive vitamin B_{12} has produced many conflicting observations, it has helped to reveal that vitamin B_{12} is absorbed by more than one mechanism

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Annotations

ECONOMY IN PRESCRIBING

THE pharmaceutical service accounts for only some 10% of the total expenditure on the National Health Service, but its high cost has been repeatedly criticised in Parliament, partly because it is one of the few main items in the N H S on which it may seem that economy can be readily effected In 1949 the average cost of prescriptions in England was 3*s*, but by the first quarter of this year it had reached 6*s* 1½*d* The increase is due almost entirely to higher ingredient costs, the corresponding average dispensing fees for the two periods were 12 05*d* and 14 68*d* Twice economy has been sought by the imposition of a charge to patients Both times the number of prescriptions dispensed has fallen, but on the second occasion, in December, 1956, this effect was quickly offset by the increased value of individual prescriptions, which jumped to the present figure from an average of 4*s* 9*d* in 1956 In June, 1957, the Minister of Health set up a committee, under the chairmanship of Sir Harry Hinchliffe, to investigate the cost of prescriptions

In an interim report, issued last Monday,[1] this committee declares that on the whole the duty of prescribing drugs has been discharged carefully and responsibly Nevertheless, some economy is possible without loss of efficiency Comparable difficulties have emerged in other countries where health services are a charge on the community In New Zealand, for instance, between 1947 and 1957 the cost of the pharmaceutical service increased by 181%, and the prescriptions per head of population increased by 65% Drastic steps were taken, and as a general rule a practitioner may now prescribe no more than ten days' supply, and some medicaments can be prescribed only on the recommendation of a hospital authority The Hinchliffe Committee contemplated calling for similar limitation here, but decided that there were too many administrative difficulties It will, however, review this possibility again in its final report

If a general practitioner does not know the true cost of his prescribing, this may be due to either of two causes—lack of training or lack of current information As a student he may never have heard of the *National Formulary*, and the committee recommends that the alternative edition, based on a pharmacological classification, of this valuable book should be supplied to all clinical students as well as to hospital doctors In the further enlightenment of the practising doctor, the regional medical officer, says the committee, should play a more active part by providing up-to-date information on developments in pharmacology and therapeutics Doctors may be entirely unaware of the cost of the drugs they prescribe, as not all manufacturers provide such information, and some five thousand proprietary products are on the market The committee suggests that the law be amended to require manufacturers to indicate the price of their products in their literature and advertisements In addition the Ministry of Health, in conjunction with the British Medical Association and the Pharmaceutical Society, should investigate the possibility of issuing a comprehensive prescribing handbook so that practitioners may have in one volume information on medicaments and their retail price and on possible alternatives

The statistics at present provided by the Ministry are inadequate and appear too infrequently Information on the cost of a practitioner's prescribing reaches him some four months after the prescription has been issued The committee maintains that this interval could be shortened if every prescription were priced individually and the present averaging system jettisoned

The committee also proposes that the Pharmacopœia Commission should be asked to review the principles on which the selection of approved names is based, and to authorise approved names more promptly But it is well known that new preparations are introduced and become fashionable through their trade names, which are coined immediately by staff employed for the purpose, and are skilfully designed to be easily written and remembered Indeed nomenclature is often ahead of the product, and at least one firm has called in cybernetics to prepare many mellifluous names which have been patented in advance The committee accepts the view, put forward by the Executive Councils' Association, that executive councils should be directed not to supply copies of their medical and pharmaceutical lists to drug houses In practice this measure would have little effect, for these are public documents, available in post offices and libraries The thorny question of substitution, well known in the hospital world, is not touched on, but no doubt it will be considered in the committee's final report

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[1] Ministry of Health Interim Report of the Committee on Cost of Prescribing H M Stationery Office Pp 12 9*d*

NEOMYCIN IN OCULAR INFECTIONS

OCULAR infections continue to contribute substantially to visual disability and blindness, despite the virtual elimination of ophthalmia neonatorum and interstitial keratitis by improved methods of treatment Most infections are exogenous, and many are associated with injury, bacteriological cultures would be expected in these circumstances to indicate the appropriate antibiotic or chemotherapeutic agent, but, owing to technical difficulties, culture specimens can be obtained only from the conjunctiva and eyelids, and in the more serious corneal and intraocular infections the organism can seldom be detected in this way Accordingly the nature of the infection must still often be determined largely by clinical deduction, and the efficacy of treatment decided by therapeutic trial or prophylaxis The value of penicillin used in these ways is evident from the greatly reduced incidence of serious ocular infections (and in particular of hypopyon ulcer) since its general use became possible, but its limitations in respect of gram-negative organisms and penicillin-resistant staphylococci are reflected in the high proportion of serious infections which are now found to be caused by these organisms Sorsby and Ungar[1] found 19 such infections in a series of 61 inpatients at the Royal Eye Hospital, and they drew attention to the need for some more effective, broader-spectrum antibiotic for use both in such cases and in prophylaxis

The choice of a broad-spectrum antibiotic presents special problems in ophthalmology owing to the selective action of the blood-aqueous barrier The comparable levels in blood and aqueous for innocuous sulphonamides are 3 4 mg per 100 ml and 0 4 mg per 100 ml respectively, with penicillin penetration into the aqueous is better, and still higher levels may be achieved by subconjunctival injection of penicillin with adrenaline[2 3]

Sorsby[1] now reports trials of several broad-spectrum antibiotics in rabbits infected with penicillin-sensitive and penicillin-resistant staphylococci and with *Pseudomonas pyocyanea* and proteus Carbomycin was perforce excluded on account of poor local tolerance, and erythromycin, which also produced some local irritation, gave unpromising results when injected subconjunctivally or given by mouth The effect of subconjunctival neomycin on penicillin-resistant staphylococci infections was more hopeful (Additional oral erythromycin produced no material extra improvement) *Ps pyocyanea* and proteus alone among the gram-negative organisms give rise to suitable experimental ocular lesions, and, with the first of these, results comparable with those obtained with polymyxin B and with streptomycin were seen Intraocular infections with proteus proved impossible to control with any of the antibiotics used, but in a parallel experiment with animals pre-treated with neomycin the infection was controlled in most cases, and in a further series of experiments with gram-negative bacteria the less fulminating infections produced by intracorneal injection of proteus were controlled A final series confirmed that in infections with the common penicillin-sensitive organisms neomycin is as effective as penicillin

Thus neomycin is no less efficacious against both gram-negative and gram-positive organisms than the other individual antibiotics Moreover it has greater range, and, being suitable for subconjunctival injection, it may be the antibiotic of choice when the causal organism is unknown Early clinical experience suggests that the human eye tolerates well the repeated subconjunctival injections of neomycin necessary to maintain therapeutic concentrations, and this antibiotic is clinically effective in severe ocular infections

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2 Sorsby, A *Proc. R Soc med* 1950, 44, 737
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NEW LIGHT ON RENAL STONES

UNDERSTANDING of urinary stone will be achieved only by appreciating the conjunction of biochemistry and mechanics which must contribute to its formation[1 2] Only biochemistry will explain why calcium salts remain in urinary solution in some individuals but not in others, and on what complex matrix the stone develops, while mechanics alone can provide the answer to where in the kidney the insoluble salts first appear and how they are eliminated thence Fortunately much of the mechanical side to this problem has already been elucidated by the work of Carr,[1] who has refined his methods still further by employing microradiography in association with freeze-drying of the specimen[3] in order to substantiate his hypothesis that renal calculi are formed on calcareous particles excreted via the lymphatic system into the renal calyx. This method has great advantages over direct radiography of the fresh specimen Fresh specimens require a waterproof layer to protect the emulsion on the film or plate; moreover, they tend to dry and shrink during exposure, it is thus difficult to obtain clarity in the ultimate picture Freeze-drying not only overcomes these difficulties but also improves contrast, since the water which is thus removed has otherwise a similar coefficient for X rays to that of the tissue itself Using fine-grain film exposed when almost in contact with the kidney at operation, Carr had previously shown small opacities in the renal substance and Randall's plaques at the renal papilla, also that an apparently solitary stone often proved to be a collection of smaller stones Now, with the aid of freeze-drying and microradiography, the story has been carried a stage further, for the plaques of calcification are seen to comprise a collection of small opacities, and Randall's plaques, likewise a granular collection of calcium salts, are observed to be lying not at the renal papilla but just beside it, where the lymphatics of the renal parenchyma discharge into the calyceal fornix Calcium does not seem, therefore, to be discharged or deposited at those parts of the renal papilla where the tubules end Furthermore, Carr has revealed that the deposition of calcium particles within the renal parenchyma is often lineal and in close relation to the vessels This new evidence strengthens his belief that deposits of calcium, like small particulate matter anywhere in the body, are transported in the lymphatic system, and in this the kidney is no exception Once projected into the renal pelvis these particles form a matrix for a larger concretion

But why do calcium salts tend to precipitate out within the kidneys of some? Boyce et al[4] have studied 148 patients with recurrent stones and have found that, though their calcium intake may differ little from that of healthy controls, their urinary output of calcium is significantly higher This may be controlled in part by a diet low in calcium and vitamin D, or by phytate administration, but these measures do not cause any distinct regression of existing stones or apparently avert further stone formation In the light of Carr's work this could hardly be

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1 See *Lancet*, 1955, ii, 1177
2 *ibid* 1956 i 1054
3 Carr, J J X-ray Microscopy and Microradiology New York, 1957
4 Boyce, W H, Garvey, F K, Goven, C. E *J Amer med Ass* 1958, 166, 1577

expected, for, by the time one stone has become manifest clinically, so many small concretions may be present that reduction in calcium intake may not reverse the process of further stone formation As Carr suggests, the only cure may then be excision of the affected lobe of the kidney Flocks [5] has also found that hypercalcinuria is common in patients with urinary stone, and yet in 21 out of 35 cases there was no evidence of hyperparathyroidism or bone disease Increased intestinal absorption may therefore be responsible—a fact which emphasises that this problem will not be solved by urologists, radiologists, or physicians alone

AMYLOIDOSIS

WHILE the cause and method of deposition of amyloid in the tissues remain unknown, the vagaries of incidence are becoming clearer In contrast to those cases in which the amyloid disease is secondary to some known predisposing cause—such as chronic sepsis, syphilis, tuberculosis, tumours, and the more recently recognised myelomatosis, rheumatoid arthritis, and regional enteritis —there are cases of " primary amyloidosis " in which no recognised cause can be found, some of these falling into definite syndromes according to the organs mainly or primarily involved Amyloid disease affecting the central nervous system sometimes escapes diagnosis [6] Chambers et al [7] report three neurological cases in which men in the early thirties developed a form of polyneuritis or symptoms mimicking tabes In the nerves there was obvious enlargement, and biopsy revealed amyloid, which was also sometimes found post mortem under the arachnoid, in the spinal dura mater, and throughout the posterior-root ganglia Chambers et al found reports of a familial form of primary amyloidosis affecting mainly the nervous system

The heart is commonly affected in primary amyloidosis, especially in older patients, the symptoms and signs are those of progressive myocardial failure, and, when no other cause can be found, amyloid disease should certainly be suspected The amyloid may be deposited extensively under the endocardium alone or also under the pericardium, or it may infiltrate the myocardium, in some cases reported by Symmers [8] the muscle-fibres were actually transformed into amyloid substance The tongue is also sometimes involved in primary amyloidosis, causing macroglossia which may lead to difficulty in speaking, eating, and protrusion As in the heart, the amyloid may be interstitial, extending out even to the gums (biopsy of which may give the diagnosis), or it may involve the muscle-fibres themselves The skin may be involved in various ways One of the patients in the series reported by Chambers et al initially consulted a dermatologist on account of trophic lesions resulting from the polyneuritis, hæmorrhagic lesions or generalised pigmentation may develop, or there may be nodular or widespread thickening due to amyloid deposition, as in an otherwise healthy young woman with involvement of the areolæ and vulva [8] The kidneys are commonly involved in secondary amyloidosis, and in the primary form hæmaturia, the nephrotic state, or even uræmia may be the only or first sign The alimentary tract is also liable to be involved in primary amyloid disease, as also in the secondary form

There was a tendency [9] to regard primary amyloidosis as a separate entity from the secondary type Besides the different distribution and the lack of a recognised predisposing cause, the primary form seemed to be characterised by different staining reactions of the amyloid deposits, and in some cases a foreign-body reaction developed around or calcium was deposited in the amyloid In a comprehensive review Symmers [10] showed that the sites involved in primary cases may also be involved in secondary, though the incidence may be very different, all the other features can occur in either form of the disease, and accordingly all varieties are related to one fundamental disturbance He suggests that amyloid is an insoluble glycoprotein laid down in the connective-tissue ground-substance as the result of a local antigen-antibody reaction Cameron [11] admits that where it comes from and how it is produced are baffling problems Both these investigators point out that amyloid is closely related to hyaline degeneration, and in biopsy some specific stain (methyl-violet, Congo-red, iodine) must be positive before the diagnosis of amyloid disease is established

STRESS FRACTURES

STRESS fractures of leg bones are often overlooked, for not uncommonly they are detectable only with special radiographic projections In the 1939–45 war, fatigue fractures of the tibia were described by Hartley [12] in children and young adults and by Leveton [13] in Army recruits In the young patient these fractures affect the upper tibia, and often spread from a small crack across the bone to produce a complete fracture In the middle-aged and elderly, fatigue fractures tend to involve the lower end of the tibia [14] Most of these patients do not give a history of unusual muscular activity, and the fractures unite fairly rapidly

In two groups of patients stress fracture seems to be an occupational hazard Burrows [15] has described a minute infraction of the tibial cortex in male ballet dancers The lesion tends to affect the middle of the bone, and gives rise to pain, swelling, and tenderness over the crest of the tibia Many different radiographs may be necessary to reveal the crack, and in two of these patients there was sufficient doubt about the diagnosis for the lesion to be explored, the specimens removed at operation showed very little evidence of bone repair A similar lesion, slightly lower in the tibia, has been described by Devas,[16] who thinks that this explains the painful condition of the leg found in athletes in training and often known as " shin splints " These patients present with pain, usually at the start of training and subsiding with rest The pain often gets more severe as training becomes more arduous, and radiographs, which may have to be repeated several times before any abnormality is detected, will show merely a small crack running through the cortex

Stress fractures in the tibia are probably a direct result of muscle pull Treatment of these minute cracks is often difficult Immobilisation is necessary only so far as it contributes to the patient's comfort In time symptoms usually subside, but the disability from this lesion is more protracted than after a complete fracture of the bone

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The Wider World

CHILD HEALTH AND DISEASE IN JAMAICA

SOME IMPRESSIONS

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With the large influx of West Indians into the cities of Britain in the past few years it has become obvious that the West Indies are very different from the tropical paradise of popular imagination Doctors, in particular those who have West Indians as patients, may be interested in a brief account of their socio-economic and medical background This is the outcome of six months spent at the University College of the West Indies, Jamaica, in 1957, as a visiting lecturer in pædiatrics and therefore has a pædiatric orientation

Jamaica is an island of great beauty and many problems The population is a million and a half and is increasing rapidly Most of the inhabitants are poor uneducated peasants engaged in agriculture The difficulties of this occupation are often great in an island where high mountains cover three-quarters of the land and plots are small and therefore uneconomical Industry is not yet a major factor in the island's economy, but the mining of bauxite is a hopeful start.

Most of the inhabitants are of African origin The 1943 Census gave

Predominantly African	78·1%
Other Afro-Caucasian or Afro-Asiatic mixtures	17·5%
Caucasian	1·1%
East Indian	2·1%
Chinese	1·0%

The dominance of the African ancestry is reflected in the Jamaican character Jamaicans, like Africans, are happy, volatile, unwilling to take life too seriously, and always ready to laugh loudly at its problems This carefree attitude is sometimes aggravating to Europeans but on the whole arouses admiration when it is set against the grim background of many of their lives Another admirable trait which must forcibly strike any doctor called on to examine a Jamaican patient is his or her personal cleanliness Not only in Britain but also in their own country, often under appalling conditions, Jamaicans keep themselves, their children, and their clothes clean and neat at all times

Family Life

Slavery was only abolished in Jamaica in 1838, and its legacy still has great influence on the peasant's life today To the pædiatrician a very striking difference between child life there and in Europe is seen in the concept of the family and particularly of the place of the father in the family The Jamaican peasant family is matriarchal and consists of a mother, often a grandmother, and several children, who may or may not have the same father More often than not there is no man in the household The illegitimacy-rate is 70%, the highest in the world. This in itself would not be serious if the parents had a stable union, but this is not often the case Many men have little sense of responsibility for the children they have fathered, and for various reasons maintenance orders are difficult to enforce. A child's idea of a father is therefore either a man who does not live at home but who may visit occasionally or a man who is resident but who is liable at any time to be replaced by another

Yet even a superficial study of Jamaican history prevents one from being censorious The first English settlers were young, tough, and adventurous, but tended to be "the black sheep of white families" They were not accompanied by white women and took mistresses from the imported African slaves, whom they did not, of course, marry. Marriage between slaves was forbidden because proprietary rights over slaves were exclusive to their owners, but reproduction was encouraged to swell the labour force This social pattern became firmly established over the next two hundred years

The children of slaves were cared for by more or less benevolent plantation owners, who themselves had unofficial as well as official families, and the children presented no economic problem to their mothers However, just over a century ago emancipation suddenly transferred the care of children to their mothers, who have had to bear a large share of responsibility for their upbringing since then The feckless attitude of many fathers today stems from the attitude of their forefathers Fortunately the idea of the father as a responsible head of the family is being accepted more widely, especially in the rising middle class

Malnutrition

The clinical syndromes of marasmus, kwashiorkor, and marasmic kwashiorkor are commonplace in Jamaica and form the background to many other diseases of childhood The social scene has, of course, great relevance to these disorders It is the mother who perforce feeds and rears the children and inevitably, no matter how hard she tries, she sometimes fails She often goes out to work soon after the baby's birth and, because of this early loss of the protective action of breast-feeding, kwashiorkor develops at a younger age in Jamaica than in Africa, where children may be breast-fed into the second or third year Many mothers work as "higglers" (pedlars), and their earnings are often very erratic A grandmother is a godsend, for she can look after the children by day, or they can reside with her for long periods Otherwise the mother has to pay a neighbour or a professional baby-minder out of her meagre earnings, and obviously in such a commercial contract the children will fare less well than if a grandmother is available

A boy, aged 9 months, was admitted to University College Hospital, Jamaica, with a vague history of "belly running" (diarrhœa) Except that his hair showed no depigmentation, the clinical picture was typical of kwashiorkor He was miserable and underweight (14 lb 10 oz.) and lost a further pound during treatment as his œdema cleared Dependent œdema was gross in his forearms, hands, legs, feet, and abdominal wall, and his face showed the characteristic "sugar-baby" jowls Flaky-paint dermatosis affected his limbs, areas of epidermis could be stripped by slight lateral pressure, and there were moist fissuring and depigmentation behind his ears, at the angles of his mouth, and in his perineum His liver was enlarged and firm His mucosæ were pale

Laboratory investigation showed a moderate anæmia, a low level of plasma-proteins, and abnormal liver-function tests A liver-biopsy specimen floated in water, and analysis gave a high fat-content.

Dietary and social history —He was breast-fed completely for four months His mother then went out to work as a "higgler", and for the next two months he received only morning and evening breast feeds, after which time breast-feeding was discontinued He was looked after by a neighbour during the daytime in company with his two siblings and several children of other working mothers The baby-minder was paid half a crown a week for his care, and his food was provided by his mother His father was not resident and contributed only sporadically to his upkeep His mother's weekly earnings varied between thirty shillings and nothing His diet consisted of 3 tablespoonfuls dried milk to 24 oz of water daily (i e, half-strength), some patent barley, corn-meal porridge (maize boiled in water and strained, often only the filtrate is given), and bush teas The latter are infusions of various wild plants and are widely used in Jamaica as constituents of a weaning diet, medicinally, or even for magical purposes Their possible toxicity is discussed below They have a negligible calorie and protein content

This history is fairly typical Sweetened condensed milk is also widely used, and quite often expensive proprietary milk beverages are given Poverty and ignorance are clearly the main factors which operate to produce such faulty feeding, but uninhibited advertising of these beverages in Press, shops, and on the radio is partly to blame by diverting money away from foods of higher protein value Meat and eggs are not given early in life, partly because of cost, but also because of a tradition that they are unsuitable at this period of life Hens may be kept, but the eggs are usually sold in the market

Severe anæmia often accompanies kwashiorkor and in many cases is unresponsive to the administration of oral iron and the correction of protein deficiency Folic acid by mouth produces a response in this group It is usually possible to diagnose folic-acid deficiency from a bone-marrow smear, whereas examination of peripheral blood is unhelpful (Back et al 1957) Peas in the West Indies have a high folic-acid content and, though they are a staple food for older children and adults, are considered unsuitable for infants and young children This difference in feeding habits in the two age-groups may explain why folic-acid deficiency is fairly common in the young child but unknown in the adult, who also often exists on a generally substandard diet

Treatment of kwashiorkor is easy in theory but often difficult in practice In bald summary it consists in the administration of dried skimmed milk in gradually increasing strengths until the patient can tolerate solid food, but this statement conceals a wealth of nursing ingenuity and patience, factors which are most important In spite of this, all too often a severely ill child dies for reasons which are at present ill understood Problems of kwashiorkor are under active investigation in Jamaica by Dr J C Waterlow and his team at the M R C Tropical Metabolism Research Unit

Malnutrition, a world-wide disease, is today rarely seen by the pædiatrician trained in Britain, and for this reason alone I felt my stay in Jamaica was worth while Two other conditions were equally striking, although they are of little relevance outside the West Indies

Veno-occlusive Disease of the Liver

This disease is fairly common in Jamaica and apparently very rare outside the island Its pathology, clinical features, and natural history have been described fully (Jelliffe et al 1954, Bras and Hill 1956, Stuart and Bras 1957) Its ætiology is less certain, but several suggestive observations and experiments on animals point to poisoning with bush teas (Bras et al 1957) The clinical picture is striking

A girl, aged 2½ years, was well until six days before admission to University College Hospital, when she became unwell and seemed hot The next day she vomited, and this symptom continued intermittently until admission She developed a "swell belly" and swollen feet on the day before admission She had had an average Jamaican diet, including three types of "bush teas"

On examination she was small and moderately well nourished Weight 22 lb 15 oz She had gross ascites, and her liver was enlarged (3 inches below the costal margin in the right mid clavicular line) and very firm Her spleen was impalpable A week after admission she developed a moderate right pleural effusion

Laboratory investigations—Liver-function tests were relatively normal, but liver-biopsy material showed the typical histological appearance of acute veno-occlusive disease (Bras and Hill 1956) Subintimal swelling of the small hepatic veins and atrophy of surrounding parenchymal cells were present Portal triads were normal

Progress—The pleural effusion and the ascites both resolved during the fourth hospital week, and the patient was discharged well shortly after this

It seems likely that one or more bush teas are responsible for the occlusion of the hepatic venous tree which causes the acute hepatomegaly and ascites seen in the acute stage The disease can have more serious consequences than this case-report suggests Stuart and Bras (1957) found that 19% of patients with acute veno-occlusive disease died of hepatic failure early in the disease, and only 48% eventually made a complete recovery Treatment at present is only symptomatic so that prophylaxis is of great importance

Unfortunately the weaning of Jamaicans from bush teas will be a very difficult task because they are very widely used indeed In fact, their omnipresence in the diet constitutes one difficulty in accepting them as the sole cause of the disease, which is certainly not so common as one would expect on this theory The difficulty is similar to that of accepting mercury as the sole cause of pink disease, or an excess of vitamin D as the sole cause of idiopathic hypercalcæmia Until recently many babies in Britain were exposed to these substances, but relatively few were affected However, if it is finally proved that Crotalaria, Senecio, or other plants are directly responsible for the condition as is suggested (Bras et al 1957), intensive propaganda will obviously be justified Many peasants use native plants indiscriminately, and children collect plants and concoct their own brews It will probably therefore not be practicable to suggest that only certain bush teas be avoided, and propaganda will have to be directed towards the habit itself, a formidable task

Vomiting Sickness

This is less common and less well-defined (*West Indian Medical Journal* 1953) Often occurring as an explosive illness in several members of the family at the same time, it is probably due to an ingested toxin, possibly the immature ackee fruit The ackee, like bush tea, is a very common article of diet, and the same difficulties in prophylaxis as with veno-occlusive disease will arise if it is proved that the immature ackee is responsible The patient may be admitted in coma after repeated vomiting lasting several hours, or, particularly in young children, coma and convulsions may develop without preceding vomiting The hepatic glycogen is scanty (Patrick et al 1955) and the blood-sugar level very low (Stuart et al 1955) Some patients make a dramatic response to intravenous glucose, but the disease can be rapidly fatal

Sickle-cell Anæmia

In a predominantly African population this disease might be expected to be relatively common, and in fact it requires consideration in the differential diagnosis of several symptom-complexes in childhood The sickle-cell trait is found in 5% of Jamaican children (Jelliffe et al 1954), and tests for sickling are therefore routine in hospital practice If the tests are positive, hæmoglobin electrophoresis is necessary to decide whether this finding is relevant to the symptoms and signs The usual features in the first two years of life are severe anæmia, fever, mild jaundice, splenomegaly, and the characteristic painful swellings of the interphalangeal joints of the fingers This description agrees with that of pure sickle-cell anæmia in Uganda (Trowell et al 1957) and has the same serious implications Clinical diagnosis is less difficult in Jamaica, however, because malaria is now uncommon Sickle-cell anæmia and other hæmoglobinopathies are also seen in older patients, and a local map of these disorders will soon emerge when the results of investigations in the hæmatology and biochemistry departments of the University College Hospital are available Unfortunately there is at present no proved effective treatment apart from blood-transfusion

Infectious Disease

Apart from the disorders described above, the pattern of disease is similar,to that which existed in Britain fifty years ago, with infectious diseases taking a relatively important role

Diphtheria is fairly common, and tracheotomy is often urgent, but, after the acute phase, recovery is usually uneventful

Typhoid fever is also fairly common, and clinical diagnosis can be difficult Rose spots are rarely seen, and splenomegaly and the so-called characteristic temperature chart are more the exception than the rule Moreover laboratory investigations are also unhelpful at times, for treatment with chloramphenicol may prevent a rising agglutinin titre

Tetanus is common, for few children in the peasant class wear shoes, and goats and donkeys are common and must be largely responsible for contamination of the soil and tracks where children walk and play Except in the neonatal form, therefore, infection usually occurs on the feet The results of treatment are not so satisfactory as one would wish, nor is it certain that orthodox methods give the best results In one hospital it was felt that the administration of repeated daily doses of antitoxin after the initial dose of 200,000 I U was important, and in others the patient was nursed in the main ward without sedation, for it was felt that spasms, although painful, were less dangerous than sedation Facilities for treatment by intermittent positive-pressure respiration after curarisation do not yet exist The various problems of treatment are under active consideration at present, and dogmatism on therapy is at present unjustified

Infantile gastroenteritis is as common as one might expect in a country with overcrowding and low sanitary standards and is more often due to Salmonellæ than in this country (*West Indian Medical Journal* 1954) Combined with malnutrition it can present a formidable problem, yet many patients recover surprisingly quickly without relapses, once initial dehydration has been overcome Persistent vomiting is common in gastroenteritis and in malnutrition Gastric lavage usually produces a large amount of mucus It is tempting and all too easy to blame this chronic gastritis and indeed many other infant maladies on such a dietetically abhorrent procedure as the administration of bush teas, but proof is lacking Vomiting does not appear to be a symptom of underfeeding in infancy as it is in this country It is common to find pure water lack in a dehydrated baby with gastroenteritis, and the practice, common in Britain, of giving an initial intravenous injection of physiological saline solution before starting the drip is contraindicated, since hyperelectrolytæmia is often present The amount of intravenous fluid required for maintenance is large—3 oz per lb of body-weight daily—and the risk of overhydration by an intravenous drip is much less than in this country Cross-infection in hospital, the main worry to the staff of a gastroenteritis unit in Britain, is uncommon in Jamaica This is fortunate, for in many hospitals segregation is impossible and gross overcrowding is the rule Cases of gastroenteritis, typhoid, and diphtheria are nursed alongside cases of kwashiorkor, sickle-cell anæmia, pneumonia, meningitis, tuberculosis in all its childhood forms, and other more familiar diseases The average age of the ward population is usually low (18 months or less), hence the freedom from cross-infection in gastroenteritis is not due to dilution of babies with older children Open windows and jalousies are necessary for comfort, and, I feel sure, are important in this respect as those working with infectious diseases in this country have insisted for years

Overt *syphilis* occurs frequently both in adults and children In adults cardiovascular syphilis is common, and it is quite justifiable to expect a West Indian student at his final examination to be familiar with the physical signs of aortic aneurysm, although this would not apply in Britain today Congenital syphilis is seen in most of its forms

Other Diseases

Acute rheumatism is surprisingly common, and there is a high incidence of vicious carditis (Back and De Pass 1957) Streptococcal infection and acute nephritis do not seem to be correspondingly common, and rheumatic nodules and chorea are rare One wonders whether subnutrition is in some way responsible for this emphasis on cardiac damage

In the educated middle class one meets the complaints associated with a higher standard of living, such as *enuresis*, *behaviour disorders*, and *obesity* The healthy child whose parents are convinced that he does not eat enough may well present in the outpatient clinic alongside the child with gross kwashiorkor *Behaviour disorders* in the peasant class are rarely seen at hospital, probably because they are not regarded as conditions requiring orthodox medical help Obeah men, the Jamaican equivalent of witch doctors, are still influential in the bush, and it is reliably reported that in some areas their permission is required before orthodox medical advice is sought

Some diseases, such as *vitamin deficiencies*, are surprisingly rare *Scurvy* probably has a similar incidence in Jamaica to that in Britain Simple *rickets* is almost unknown in spite of the grossly inadequate diets, which must be deficient in vitamin D In general, rickets is not rare in the tropics (Jelliffe 1955) and is usually due to traditions, such as swaddling and nursing in purdah, which lead to inadequate exposure to sunlight There are no such traditions in Jamaica The classical signs of deficiences of the vitamin-B group are uncommon, although such diseases might be expected in view of the central place of degerminated maize in the diet

Infantile pyloric stenosis is very rare, so much so that the occurrence of a case is an event in hospital practice

Neonatal Disorders

Infant mortality is high (78 per 1000 in 1951), and a large proportion of deaths is due to infection Other causes of death, operative mainly in the neonatal period, are much less important, in hospital at least, the neonatal period seems relatively safe For instance, labour is easy, during my stay I saw no baby with signs of cerebral birth injury in the obstetric department of the hospital

Prematurity, defined by birthweight, is common, but for a given weight a Jamaican premature baby is much more mature in behaviour than his European and North American counterparts Problems of temperature regulation, initiation and maintenance of respiration, and feeding are much less obtrusive than in Britain A 3-lb baby, for instance, will often take well from the breast and cause little anxiety to the nurses Relative behavioural maturity has recently been demonstrated in newborn babies in Uganda (Geber and Dean 1957)

Hæmolytic disease of the newborn is relatively uncommon, for the proportion of the population which is rhesus-negative is about half that in Britain

To the pædiatrician, then, neonatal work has less clinical interest than it has in this country

Feeding difficulties in the early months are also few Breast-feeding is widespread, on demand, and there is no false modesty about it among most mothers In such a poor country the natural method is often the only adequate method, and it is fortunate that breast-feeding is so easy for nearly all women It is sad to see the influence of advertisements for dried milk on such people The idea that breast-milk is inferior to these products is easily induced, and dried milk may be deliberately substituted for breast-milk by a mother because she understands it to be superior, although she will probably dilute it to make it last longer

Preventive Pædiatrics

It will be clear that Jamaica is no Welfare State Government medical services are mainly curative and, although the Hyacinth Lightbourne Nursing Service combines preventive and curative work in an admirable way, there is a great need for health visitors and infant-welfare clinics Diphtheria, whooping-cough, and tetanus are far too common, and there is a danger that they will continue to be accepted as inevitable because they have no news value today Poliomyelitis, by contrast, has been in the limelight recently, and in 1957 a widespread official inoculation campaign against it was undertaken in Jamaica, although in terms of mortality it has so far been no more important than the other diseases

The main problem of preventive pædiatrics in Jamaica, of course, is malnutrition The issues here are mainly economic, and its discussion is beyond the scope of this article At present UNICEF provide free skimmed dried milk to this and other countries who need it, and it is available to mothers in certain areas at a price equivalent to the cost of distribution There is a danger, however, that this very laudable arrangement will officially be taken for granted and no provisions made if the supply ceases In spite of poverty, education and encouragement can achieve much in the prevention of malnutrition It was surprising how often patients, admitted to hospital with kwashiorkor, continued to thrive after discharge from hospital although the economic circumstances were unchanged A comprehensive health-visitor service could go some of the way in preventing malnutrition

I wish to thank all those, too numerous to mention, who made my stay in Jamaica so enjoyable and educative It is to a large extent the observations and opinions of the doctors, nurses, and students of the University College Hospital and the Kingston Public Hospital which are embodied in this article Any errors must be ascribed to myself, the visitor, whose only advantage was possession of the opportunity to see diseases and situations with a fresh eye Finally, I wish to thank Prof J M Smellie, the University of Birmingham, and the British Council for making the visit possible I hope that such visits to tropical countries will become more general, for it is difficult to exaggerate their value

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Public Health

NOTES ON SMALLPOX VACCINATION

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THE work on which these notes are based was undertaken, in the first instance, to demonstrate to students the technique of multiple-pressure vaccination

The Site

There are certain disadvantages in the accepted methods of administering the vaccine, the chief of which is the site favoured—the deltoid region This is an inconvenient area Except in the case of babies, coats have to be removed and shirt and other sleeves have to be rolled up and held in position over the shoulder, and these garments have to be replaced without disturbing the lymph All this has to be done again later for medical inspection and for any local treatment that may be needed

There is no valid objection to vaccination on the anterior surface of the forearm, where a Schick test is done The vaccine can be inserted much more easily with the operator sitting opposite the seated patient, and greater control can be exercised in stretching the skin and making the required pressures, and after control is also much easier An additional advantage in females is the cosmetic effect any scarring in this area is minimal and is practically never seen in ordinary circumstances

Expulsion of Lymph

It is sometimes difficult to expel the lymph from the capillary tube in which it is supplied An ingenious method of overcoming this difficulty was described by Galpine (1951) One of the broken ends of the tube is inserted into the bulbous end of an ordinary rubber teat, into the open end of the teat a glass tube, lightly plugged with sterilised cotton-wool, is inserted, and the lymph may then be expelled by gently blowing through the glass tube

This was found to work very well in practice, affording a great deal of control, but occasionally it was impossible to avoid expressing an excessive amount of lymph This difficulty was overcome by what appears to be an even simpler procedure The capillary tube is broken in the usual way with due asepsis, it is then held vertically between the thumb and the first finger, while the hypothenar aspect of the hand is tapped against a hard surface—e g , a table This brings the lymph down to the open lower end of the tube The tube is then very gently tapped against the surface of the prepared skin and, by capillarity, a small amount of the lymph comes out.

This method allows a very great deal of control of the quantity of lymph used and may prove very economical when large numbers of people have to be vaccinated Vaccinating a class of medical students I set out to ascertain how many could be vaccinated with a single tube I had got as far as vaccinating nineteen when a tiny speck of blood was observed contaminating the lymph The risk of transmitting viral hepatitis caused me to reject the remainder of the lymph, but I think there would have been no difficulty in bringing the number of vaccinations with that tube up to twenty-five.

Multiple-pressure Vaccination

In describing the multiple-pressure methods all the textbooks teach that the drop of lymph should be placed on the skin first, and the pressures of the needle made through it, but I experienced some difficulty in practising this method without drawing blood at the same time The viscosity of the lymph seems to protect the skin and thus calls for undue pressure of the needle, which therefore occasionally goes deeper into the skin than it should. To overcome this difficulty the following method was devised in which the necessary pressures are made before the lymph is applied

(1) The skin of the anterior surface of the forearm is prepared in the usual way, acetone being used for surface disinfection

(2) The operator next takes the capillary tube and breaks off each end in turn, using two sterilised pairs of forceps guarded with sterilised rubber tubing The lymph is brought to one end in the manner described above, and the tube may then be handed to an assistant or laid aside for the moment

(3) The operator then grasps the posterior aspect of the patient's forearm with his left hand and puts the skin on the stretch. Next he taps the tightened skin very gently with a no 1 straight Hagedorn needle Soon the altered appearance of the skin indicates that the necessary breach in continuity has been made the opaque silvery appearance is quite distinctive

(4) For the needle is substituted the capillary tube with the lymph shaken well down. The tube is tapped, again very gently, on the abraded surface, which is soon covered by a film of lymph whose thickness depends entirely on the number of taps At this juncture the platinum spatula of an old vaccination scarifier is used for pressing the lymph gently into the underlying cells of the cutis vera.

(5) The lymph is allowed to dry before the patient's sleeve is pulled down, and the operation may then be regarded as complete Some operators prefer to apply a dressing, in this case the only precaution needed is to make sure that an antiseptic one is not used.

It is, of course, assumed that strict asepsis is observed throughout the procedure

This method has been used in 255 adults, of whom 89 were medical students, and 244 of the vaccinated persons were followed up The after-effects differed in no appreciable way from those observed in the case of ordinary vaccination in the deltoid area The ease of examination was an outstanding advantage, as was the ease of applying either stupes or penicillin cream in the few cases of primary vaccination in which the local reaction called for treatment A further advantage was the facility with which the various stages of the lesion could be studied, this was much appreciated by the students

Vaccinia

The result of inoculating cowpox into man depends almost entirely on the patient's previous vaccination history A person who has been vaccinated more than once previously nearly always develops an immune reaction (papule formation alone without any general reaction) An adult who was vaccinated only once in infancy may develop a typical primary vaccinia or an accelerated reaction, but usually little or no general reaction or only a fleeting one In an adult who has never been vaccinated the picture is quite different, the cooperation of medical students in this inquiry has offered an opportunity of studying it closely

The conclusion that I am forced to is that vaccination should not be regarded lightly in such cases, and most certainly not the reaction which almost invariably develops after it. The peak effect, however, does not endure more than two or three days at the worst, and the patient should be warned that this will be experienced about the tenth or eleventh day, and that, no matter how bad he may feel, he will eventually recover

The notes made for me by my students indicate that there is a primary viræmia, which may occur between the fourth and seventh days, but that the brunt of the attack (corresponding no doubt to a secondary viræmia) falls between the tenth and the twelfth days Usually the reaction is severe, being ushered in by malaise, shivering, nausea, and prostration Pyrexia is an invariable accompaniment, in 1 case it was 103°F, but it is usually about 101°F At this stage lymphangitis is prominent, lasting during the pyrexia and subsiding with it, forearm vaccination afforded a very good opportunity of observing this Myalgia and headache also were prominent. In addition to the zone of hyperæmia immediately adjoining the nodal point, widespread erythema may affect the limb, in 1 case (the only one to cause apprehension) there was, in addition to the erythema, a bullous eruption involving the forearm and the upper arm Pyrexia in this case was high—100°–103°F for four days—after which the condition subsided, and recovery was uneventful Axillary adenitis was observed in practically all the cases Apart from the last-mentioned patient (who was confined to bed for a week) the longest period of rest in bed was three days

Of the 89 students the vaccination was primary in 20, of whom 16 presented the severe type of reaction In none of the remaining 69 students was the reaction such as to require treatment in bed or to interfere with their ordinary activities except, perhaps, sport for a few days

Much the same can be said of 166 other persons vaccinated Most of these came for vaccination because they were proceeding abroad In addition I saw a very much larger number who had been vaccinated by their family doctors and had to present themselves to me, as city medical officer, for authentication of their vaccination certificates

It seems inevitable that there will be a further dispersion of people to countries where smallpox is a risk or in which the health authorities require vaccination as a prerequisite for entry In view of the unpleasant reactions inseparable from primary vaccination in adults it must be regarded as a great folly to postpone this procedure in infancy

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Special Articles

AUSTRALIAN SCHOOL OF MEDICAL RESEARCH

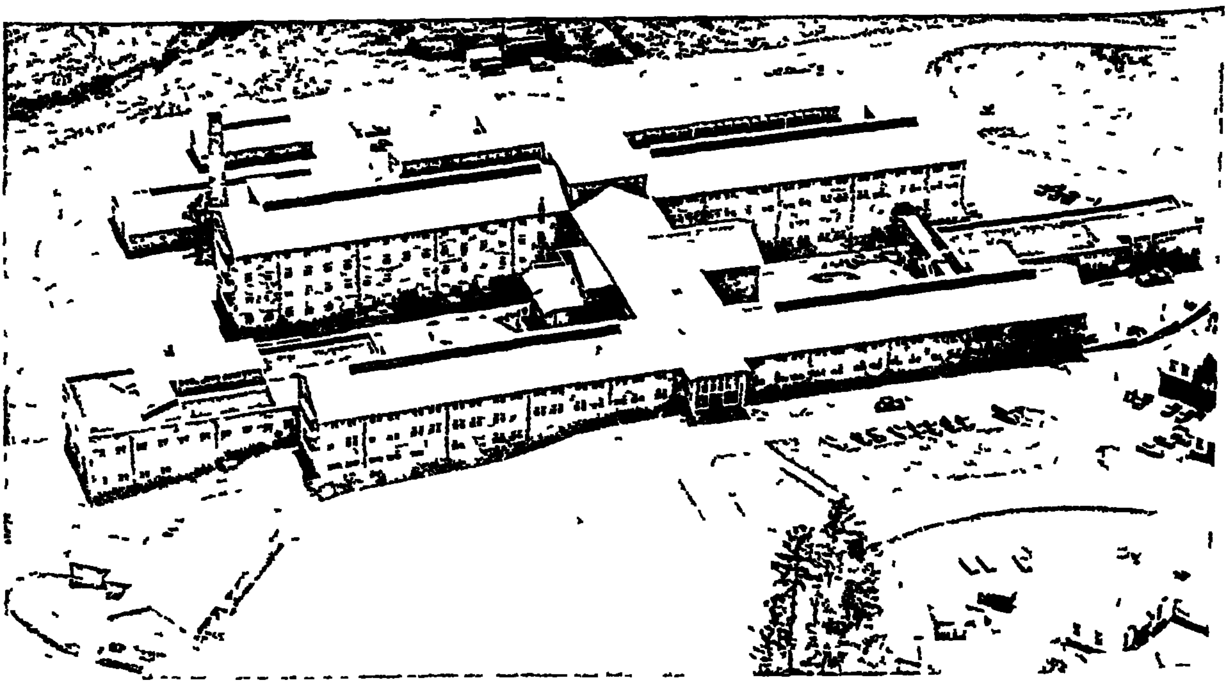
In 1946 the National University of Australia was founded as a national centre for research and research training It was Australia's constructive response to the complaints that many able scientists left the country to study and work at universities and institutions in Great Britain This depletion was most sharply felt in the medical sciences, for at that time the only Australian medical research institute with an international reputation was the comparatively small Walter and Eliza Hall Institute in Melbourne As long ago as 1944 Sir Howard Florey, himself an Australian graduate, had suggested in a report to the Commonwealth Government that a national institute for advanced medical sciences should be set up This project was accordingly included in the early plans of the new university, and until 1955 Sir Howard Florey was adviser to the council of the university in the establishment of the John Curtin School of Medical Research Last March, at Canberra, in the presence of the Australian Prime Minister, Sir Howard formally opened the buildings which are to be the school's permanent home

From its earliest days the school has thus had his support and counsel, and at its inception it followed his wise suggestion not to let men wait on bricks and mortar and in 1948 appointed professors to establish the first departments though there were then no laboratories in Canberra The departments were started in laboratory space lent by several institutions biochemistry at the Commonwealth Serum Laboratories in Melbourne, medical chemistry at the Wellcome Research Institution in London, microbiology at the Walter and Eliza Hall Institute in Melbourne, experimental pathology in Sir Howard's laboratories in Oxford, and physiology in the University of Otago in New Zealand In 1951 temporary laboratories were built in Canberra, and these were occupied between 1952 and 1957, when the departments moved to the present building

The school stands in $6^{1}/_{2}$ acres of ground within the university site, looking towards the Brindabella range It is a brick building about 170,000 square feet in floor area It is built in an H-shape, with four wings for laboratories (which are mainly on the upper two floors) and a central spine housing lecture theatre, seminar rooms, offices, tearooms, and library The lower floors house many of the service departments store, photography, media kitchens, mechanical plant, and so on There are also two animal houses, each of some 7000 square feet floor area, one for non-infected and the other for infected animals, an animal breeding establishment some four miles away, and a large light-engineering workshop

The laboratory wings have on the south side laboratories 20 ft deep and on the north side service rooms (hot rooms, cold rooms, &c) and studies 14 ft deep The laboratory layout on each floor is adapted to the needs of the particular department, but within the departments it follows a standard plan

At present there are five departments Prof A H Ennor is head of the department of biochemistry, and also dean of the school Dr F C Courtice has just been appointed to the chair of experimental pathology Prof Adrien Albert is director of the department of medical chemistry, Prof F J Fenner of the department of microbiology, and Sir John Eccles of the department of physiology At present the total research staff is about 40 and there are some 20 PH D students, but the school is still growing Several new departments will be started over the next few years to fill gaps in the present structure, and each department will be developed



In England Now

A Running Commentary by Peripatetic Correspondents

On Tuesday, at Westminster, the Royal Army Medical Corps celebrated its diamond jubilee with all the national splendour of an Abbey service After the entry of Queen Elizabeth the Queen Mother, colonel-in-chief of the Corps, a fanfare echoed exquisitely in the roof, the National Anthem was sung, and the Dean bade us join in "an act of thanksgiving, remembrance, and dedication" But amid so much that was beautiful, nothing was more appropriate than the breathtaking sight of the great nave filled with men in battledress—recalling so directly the medical services in action and the armies they have served. As the Chaplain-General said in his sermon, the R A M C has no battle honours of its own, but has a share in the battle honours of every regiment

* * *

After seeing her off on the last bus, I went to collect my cycle from the cycle-park There were still many cycles there and it took me a little time to find it. I reached out to pull it down from its rack, but there was an unfamiliar resistance—the back wheel was padlocked At first I had grave doubts as to whether the cycle was really mine I walked the length of the park looking searchingly at each cycle, then back again—no, it was mine. I gazed at the cycle forlornly and at the strange chain that bound it How had it got there? How should I get it off?—it was a stout chain and stouter lock

I gave it a smart tap with my shoe which I took off for this purpose I looked guiltily around and replaced my shoe Nobody would believe it was my cycle I tried all the keys in my pocket although I knew they would not fit Perhaps the law had put it on—the cycle wasn't really fit to be on the road If I ever freed it I vowed I would have new brake-blocks and tighten up the front wheel Feeling increasingly guilty I took a safety pin from my lapel and fiddled with the lock, hastily changing tactics and pretending to be adjusting my cycle-clips as other callous riders easily gathered their cycles and rode off

It was dark and cold I was far from home I couldn't possibly trundle it back holding up the back wheel the whole time In despair I approached the next person who showed signs of retrieving a cycle I explained my plight. It did not sound very true I felt very guilty I wondered if he would report me A night in a prison cell seemed possible He did not say anything, took the proffered pin, inserted it in the lock, and in a trice the cycle was freed. I thanked him profusely, took down my cycle feeling as if I had stolen the Crown Jewels, and rode off The strange chain was in my pocket—I would have to get rid of it at the earliest moment

I laughed to myself I wondered what the owner of the chain would think when he found his cycle safe but unshackled I let myself in through my back door and opened the cycle shed—inside was my cycle I remembered then I had of course set out by bus

* * *

My life-work is nearly at an end I have all but completed my great Contribution to scientific thought and achievement Only one thing is exercising me—*the title* I wrote the title in my mind at least 17 different ways before the first word of the thesis ever hit paper, but indecision, like choreopsis, set in and I am as far from fixing it as ever Must hurry up or someone else will publish first The obvious thing is a clear straightforward descriptive honest sort of title that tells at a glance just what it is all about, like "A Textbook of Endolymphology", except that it isn't that, or "Modern Trends in Cervical Prostheses", but it isn't that either Applying this to mine would make it something like "Some Aspects of the Dihydrophyllobothrium Reaction in Anxiety-hysteria related to Lesions of the Caudate Nucleus in Ovariectomised Albino Rats when compared with Staffelhagen's Procedure in Brazilian Long-tailed Monkeys", which no subeditor would pass unsubedited It's a good title in its way, but admittedly it lacks punch, offers no positive incentive to the reader

Rooting myself in tradition I have looked over some of my great-grandfather's books, but "On Afthma—being a Comprehenfive Difquifition upon itf Caufe, Prevention, and Cure Ufing Diverfe Phyfic, Second to None in the Britifh Empire" somehow doesn't sound quite right, even if I did change the wording to suit my rats Or I might go all Transatlantic and come out with a challenging title like "Does Phyllobothrium Make Rats Anxious?" or, even more challenging, just "RATS!" Then there's the possibility of something allegorical like "Rats through my Crystal Ball", or I could borrow something from the classics like "To Grunt and Sweat under a Weary Life", subtitled "The Experimental Rat in Times of Trouble"

On the whole I think I had really better leave rats out of it, other people don't like them as much as I do, and maybe a mention in the title might not make the impact on the general reader that it ought It must be something *attractive*, to make people sit up and get half-way through before they realise how shatteringly dull it all is Then my name will be indelibly printed on their minds as that bloke who did the unusual work on anxiety How about "A New Approach to Anxiety"? Better, but people shy off these psychiatric-sounding words I ought to stay organic perhaps a snappy combination would be the thing, like "The Relation of Lesions of the Caudate Nucleus to Anxiety", which sounds much more as if I've got to the root of something "The Caudate Nucleus and Anxiety" ? ? Oh! I don't know maybe "Rats!" was best after all

* * *

The politicians seem quite unworried about my grandchildren As Woomera, Cape Canaveral, and (until recently) somewhere in the tundra have been assaulting their genes, I have a clear responsibility to counter with firm defensive steps In my favour is the fact that their mother is now, rather proudly, 4 My least responsibility is to try to offer her children correct closure of their cardiac foramina and ductuses, and early spring seemed a convenient time to channel the german measles virus our way

The bush-telegraph duly reported Victoria on the first day of her rash My wife regarded this as a strictly clinical occasion, calling for the proper case-management of this obverse preventive medicine Other families clearly thought the responsibility lay elsewhere Victoria, surrounded by attendant mothers with an improbable number of daughters, sat nauseated but happy, accepting ever more chocolate which seemed to be the correct, the conventional, or, perhaps, merely the ritual offering There was a chorus of "Now, kiss *poor* little Vicky with her spots"

It wasn't my fault that nothing happened, nor am I in any way to blame that a chance contact a couple of weeks later produced real measles Perhaps medical training has unsuited me for causing disease

* * *

PERIPATETIC PRACTICE

I went to see my doctor
  (There were three partners more)
But I forgot that it was not
  His one weekend in four

I rang up a physician
  But found he was away
At some immense world conference,
  Somewhere in U S A

I rang up a chirurgeon
  Reply came "Not at home,
Some day this week he's due to speak
  At Brussels or in Rome"

The thought comes to my brain
  When next I have my pain
All on my own I'll telephone
  Health-Castle One, in Spain.

Letters to the Editor

THE RUSSIAN VACCINE

Sir,—The letter by Dr Liversedge in your issue of June 7 draws attention to the very troublesome situation which has developed following the publicity which has recently been given in the Press and in Parliament to the Russian vaccine

Like him we have had a large number of requests from despairing patients and their relatives for treatment with this vaccine and it has been difficult to make them understand just how speculative this treatment is and how unlikely are the chances of cure Even if disseminated (multiple) sclerosis is regarded as a virus disease it would be unique if injection of its killed virus brought about a cure once the disease was established

Two years ago, by the courtesy of Professor Sarkisov of Moscow, we received a quantity of this vaccine and since then we have used it in the treatment of 14 patients who had disseminated sclerosis (11 in the Western Infirmary and 3 in private) In all patients a full clinical history was taken and a careful assessment made of the nervous damage Before treatment was started a full explanation was given to every patient and his or her relatives of its experimental nature and our doubts of its efficacy In accord with the instructions provided, an intradermal test using 0 2 ml vaccine was done, as those showing a marked reaction should have intradermal vaccination and negative reactors should have larger dosage subcutaneously Of our patients only 4 showed marked local reactions, 2 of these were early acute cases and 2 were of several years' duration Because of the limited amount of vaccine at our disposal, and our very tenuous information as to its composition and toxicity, it was decided to treat all the patients of this first series intradermally

Of our total of 14 cases, 1 has since died of intercurrent urinary infection, and 3 are now bed-ridden 4 patients state that the treatment has had no effect on their illness and 6 claim to be improved A careful examination of these six patients shows no objective evidence of improvement of the nervous damage Of these 6 patients only 1 had a marked primary local reaction to the vaccine, and they included both early and late types of the disease In another case—a young girl with acute disease and a strongly positive skin reaction—evidence of spreading damage to the nervous system was obvious during and after treatment

We think, like Dr Lhermitte of the Saltpetriere, that these results could hardly be regarded as encouraging

The recent statement by Professor Dick that injection of the virus into animals was followed by the appearance of Negri bodies in the brain is certainly disquieting At least we can say that so far we have not encountered any definite deleterious effect

In a disease like disseminated sclerosis in which spontaneous remissions and exacerbations are the rule, and in which there is very often a large functional overlay, it is very difficult to assess the value of any form of treatment unless it is applied to a number of cases over a long time If this vaccine has curative properties we feel that out of our 14 patients we should have had at least 1 or 2 definite successes in the two-year trial period

The criticism may be advanced that our results in some cases would have been different if we had used larger doses subcutaneously We can only say that we observed no variation in results between those who had a marked local reaction to begin with and those who did not react at all

When any new form of treatment for disseminated sclerosis is suggested in the medical or lay Press it is understandable that many hopeless sufferers will immediately feel that they must try it We are familiar with many of these unfortunate essays in the past—the organic *arsenicals, protein shock, globoid bodies,* liver extracts, and latterly the copper salts To prevent sad disappointment and possible exploitation we feel that either this vaccine should be rejected as valueless and possibly dangerous or that some organised and well-controlled trial of it should be made before it is distributed Our own observations are being continued

The Western Infirmary,
Glasgow

J A W McCluskie
Gerald C Timbury

BLUNDERBUSS WOUND OF THE ABDOMEN

Sir,—Gunshot injuries of the abdomen are still rare enough in central London to excite interest The case here reported—an injury by a blunderbuss—is probably unique during the past hundred years, and research by the firearms department of New Scotland Yard has failed to discover any parallel instance This report is made because of the unusual circumstances of the infliction of the injury rather than because it has any particular or important contribution to make to the surgery of trauma

A man, aged 58, was admitted to the Middlesex Hospital on June 30, *1949,* in emergency, with a penetrating gunshot wound of the abdomen Since he was shocked and bleeding steadily from a 1 in puncture wound at McBurney's point, he was transferred immediately to the operating-theatre where resuscitation was started No exit wound was found, and a plain radiograph showed a ball lodged on the surface of the ilium (see figure) Since rapid transfusion did not produce correspondingly rapid clinical improvement, operation was performed on the assumption that he was bleeding from mesenteric vessels Through an oblique incision, excising the wound, a large laceration of the mesentery was dealt with The terminal ileum had been breached in two places and the ball was located by the finger of Mr L Atkinson, who was assisting; the ball was embedded in the iliacus muscle immediately lateral to the right ureter, which was undamaged The ball was removed and the gut repaired No efforts were made to search for the accompanying debris, save what could easily be seen or felt Two large drains were inserted through separate incisions and the wound was closed The patient received the standard "battle" postoperative treatment of those days—i e, suction and intravenous therapy, anti-tetanus serum, anti-gas-gangrene serum, soluble sulphonamides, and penicillin There was no obvious gross infection, and he had two spontaneous bowel actions on the fifth day Two years later, in 1951, he needed repair of a small incisional hernia through one of the drainage openings Following this he was free of the symptoms of wind and distension which he had had since his injury He remains well

Shot from blunderbuss

The story of the wound is this

An eminent consulting surgeon, having attained his well-earned retirement, was moving from his house in the Harley-Street area Having no further use for an old gun which had adorned his wall he presented it to his manservant, who, delighted by this evidence of his master's regard, bore it down to his basement workshop to furbish it up. It was a brass-finished, bell-mouthed blunderbuss of percussion-cap type, and since the touch-hole did not yield to simple probing, the patient decided to burn out the occluding debris with a blow-lamp. He did this in his vice and then laid the gun down with the barrel pointing towards him and the butt pointing away from him further to clean out the bore. At this point, to his surprise, it went off. The ball was 1¹/₄ in. in diameter and was composed of multiple small segments of rusty iron, resembling chopped-up nails fused together by lead.

The former owner of the gun later made an interesting point. It had previously hung in the house of his mother in Ireland and had never, to the knowledge of anyone in the family, been used or touched. It is probable, therefore, that the loading dates back up to a hundred years, since balls of this type were not readily obtainable even in the more recent "troubles". This long lapse of time between loading and discharge is, though not unrecorded, unusual, and would seem to raise a point of what, for want of a better term, may be called preventive surgery. Despite the efforts of our export trade there may yet be a few antiques remaining in this country and some weapons among them. It would seem prudent for an owner of such heirlooms gingerly to insert a ramrod down the muzzle and to compare the internal with the external length of the barrel to the touch-hole or flash-pan. If a discrepancy exists it might be wise to seek the advice of a gunsmith. On no account should a "do-it-yourself" attempt be made to withdraw the charge.

London, N.W.1 J. H. LEES FERGUSON

HÆMORRHAGIC DIATHESIS AND OVARIAN DEFICIENCY

SIR,—The problem of hæmorrhagic diathesis in association with ovarian dysfunction, rather than deficiency, has interested me keenly for some time, and this interest was lately enhanced by Dr. Wells' article in your issue of April 26. However, before accepting the proposition that the case he describes is a hæmorrhagic diathesis due to ovarian dysfunction, or that more nebulous condition "hormonal imbalance", I think several points must be decided.

First, the "atrophic" ovary never reached the pathologist for microscopical inspection, ovaries are notoriously difficult to assess from a functional point of view at laparotomy, and section is the only way to ascertain whether or not there is any activity of the follicles. Even this can give only limited knowledge and until serum-hormone assays can be done routinely it will be extremely difficult to accept naked-eye reports of functional activity. Furthermore, one ovary may not be as good as two, but many women manage normal function on a single ovary, I do not think the absence of the patient's right ovary should lead Dr. Wells to assume any degree of hypofunction in the contralateral organ.

My second point is somewhat similar—namely, that neither anatomy, histology, nor cytology give much indication of absolute function. My own experience of these cases, from a laboratory point of view, is that although the platelets show normal morphology they are not functionally fully active, and this is borne out by the work of P. de Nicola et al. (personal communication). They showed that during the normal menstrual cycle there is a marked fall of platelet activity just before, during, and immediately after menstruation, my own findings were that in menorrhagia some women maintain this state of depressed platelet function for as long as the bleeding may last, and at times for considerably longer. All sorts of vicarious menstruation may also be met with during this period of platelet dysfunction. This can easily be assessed by serial thromboplastin-generation tests, using a standard count of one million platelets per 0·1 ml. in the test and comparing it with a similar number of control (normal) platelets. Dr. Wells does not make any mention of platelet activity, which, to me, appears to be a major omission. He also states that the patient's plasma was mixed with varying proportions of normal plasma and no coagulation defect found if, as one assumes, the patient's plasma was platelet-free or platelet-poor, this is not a surprising finding. It is a pity, therefore, that no evaluation of platelet function, per se, was attempted.

Thirdly, the difficulty of controls if women with and sometimes without menorrhagia are subjected to Hess's test, a fair proportion will be found to be positive. This is the difficult point for interpretation, Stefanini and Dameshek [1] state that œstrogen increases capillary fragility and permeability, Salvatore [2] found that the capillary fragility was increased during normal menstruation, at which time there is an alleged withdrawal of the ovarian hormones. Nevertheless, there are well-authenticated cases of purpura simplex occurring at the time of menstruation. The permeability of the capillaries, both endometrial and general, is no doubt influenced to a great extent by various hormones, and Dr. Wells has given us another example of this by showing that the capillary permeability can, in some or occasional cases, be controlled by judicious hormone therapy. This is, in my opinion, the main value of his article on this vexed but fascinating subject.

East Fremantle,
West Australia A. K. FRAZER

THE DANGEROUS WATER-STERILISER

SIR,—May I enlarge upon the noteworthy summary given by Dr. Behr (June 14) of the dangerous defects he has observed in tank forms of water/saline autoclaves in connection with outbreaks of theatre infections?

A large proportion of these tanks at present installed in the surgical theatres of this country are not in fact sterilisers but merely steam-coil boilers (disinfectors) working at less than 100°C, in addition these boilers possess no safeguard against recontamination by any one of several routes.

Three different makes of water/saline tank-form autoclaves were examined recently, apart from automatic control, they incorporated all modern developments in design including (*a*) automatic cleaning and sterilisation of the air filter and the water level gauge glass during each sterilisation run, (*b*) means to prevent recontamination of the tank contents from a leaking filler valve, and (*c*) attachments for sterilisation of the outlet faucet whenever required.

Each autoclave was designed for mains steam only and was operated by means of hand stop valves, cooling coils were fitted to the "hot" as well as to the "cold" tanks. The minimum number of stop valves to be manipulated during routine operation was 6 (12 for each pair) but, in addition, there were at least 4 further stop valves (8 per pair) to be manipulated when necessary. Though these sterilisers were of the most highly developed hand-operated designs—and costly in consequence—their operation was found to be too complicated and time-consuming for use in busy modern theatre suites. Further the continued sterility of the contents could not be assured since no stop valve remains bacteria proof and continual re-sterilisation of the outlet faucet proved impracticable, even the incorporation of automatic control would not have circumvented the latter difficulty. This confirms Dr. Behr's conclusion that "only a bottled supply of autoclaved water can be guaranteed to be sterile".

For this reason and influenced no doubt by the findings of Walter [3] and Perkins,[4] tank forms of autoclave are being replaced in both the New World and on the Continent by a system evolved for the supply of all theatre sterile fluids in bottled form. The plastic pouring lip of each glass bottle is maintained in a sterile state by means of an easily removable cap. A suitable stock of fluids is maintained in the theatre itself

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1. Stefanini, M., Dameshek, W. The Hemorrhagic Disorders. New York, 1955.
2. Salvatore, C. A. *Surg. Gynec. Obstet.* 1952, 95, 13.
3. Walter, C. W. The Aseptic Treatment of Wounds. New York, 1948.
4. Perkins, J. J. Principles and Methods of Sterilisation. Oxford, 1956.

and bottles for immediate use are stored in warming cupboards automatically maintained at requisite temperatures—e g , 82°C for hot packs

I feel sure that in his introductory paragraph Dr Behr does not intend to lend countenance in any way to the use of inefficient dressing sterilisers—e g , those with inadequate air filters through which, after sterilisation, the load may be recontaminated not only by pathogenic spore-bearing species but also by coccal organisms [5]

Royal Infirmary,
Edinburgh

J H Bowie

THE ROLE OF VITAMIN B_{12} IN CARBOHYDRATE METABOLISM

SIR,—Since the discovery of cyanocobalamin (vitamin B_{12}) in 1948, and its crystallisation, it has been found to have not only anti-anæmic but also neurogenic and metabolic functions

We now suggest that vitamin B_{12} is concerned in carbohydrate metabolism, probably through the synthesis of glutathione, which was found in reduced amounts in the red cells in pernicious anæmia in rats deficient in vitamin B_{12} These rats were also less able to reduce glucose to ribose than normal rats [6, 7], ribose is important in carbohydrate metabolism as it enters into the adenosine phosphates (mono, di, and tri) which enter into the process of breaking down glucose to pyruvic acid through many steps Ribose also enters into the formation of coenzymes I and II, which are essential for further breakdown of pyruvic acid to CO_2 and water [8] Further evidence of the relation of vitamin B_{12} to carbohydrate metabolism lies in the fact that it abolishes the hyperglycæmia induced in rats by cortisone or large amounts of glucose [9]

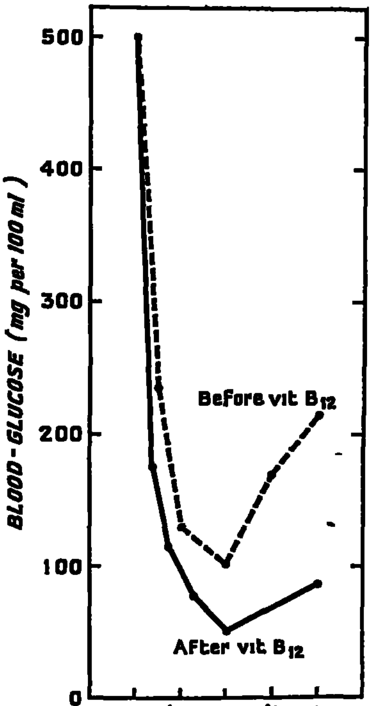

Fig 1—Insulin-sensitivity test.

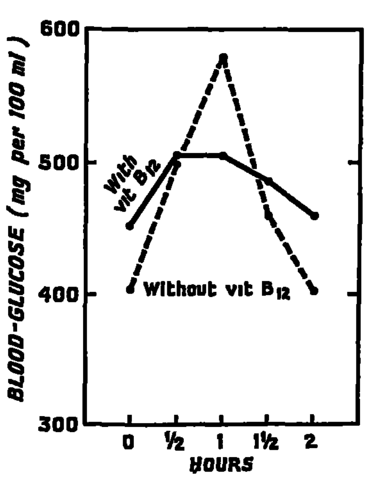

Fig 2—Intravenous glucose-tolerance curve

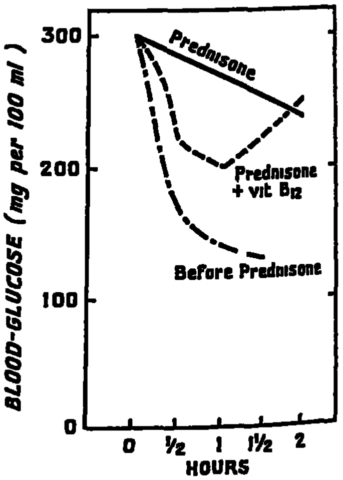

Fig 3—Insulin-sensitivity test.

In the light of this and of the current trials of vitamin B_{12} in the treatment of diabetic neuropathy, it has occurred to us to study the role of this vitamin in carbohydrate metabolism, both in normal people and in diabetic patients, where there is disturbance in this metabolism. The following experiments were carried out in 28 patients admitted to the department of medicine

Insulin sensitivity—Insulin sensitivity was tested, then 1000 µg of B_{12} was given daily for two days and the test repeated Of 20 subjects, 15 became more sensitive to insulin than before receiving B_{12} with a drop of between 30 and 150 mg of glucose per 100 ml (fig 1)

Intravenous glucose-tolerance curve—This test was done with and without the addition of 1000 µg of B_{12} intravenously, in an attempt to find out whether any possible action of it is through the liver directly The curve became flatter in 4 out of 5 cases (fig 2)

Hyperglycæmia—The effect was observed of vitamin B_{12} on the glucose-tolerance curve and insulin sensitivity in 5 diabetic patients and 3 normal people made hyperglycæmic by prednisone The glucose-tolerance curves became more normal on B_{12}, and the subjects became more sensitive to insulin—i e , the hyperglycæmia induced by prednisone was partly abolished by B_{12} (figs 3 and 4)

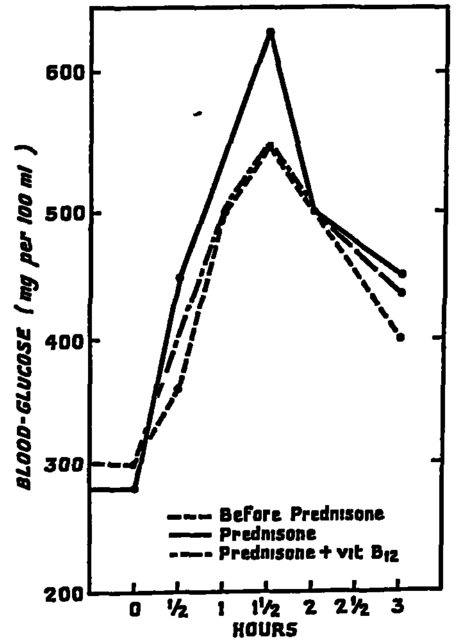

Fig 4—Glucose-tolerance curve

These results may possibly be explained through the following mechanisms

1 Vitamin B_{12} is important in the formation of adenosine triphosphate, which is essential for phosphorylation of glucose, and as insulin also probably acts on this stage through acti-

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5 Howie, J W , Timbury, M C *Lancet*, 1956, ii, 669
6 Ling, C T , Chow, B T *J biol Chem* 1952, 198, 439
7 Ling, T , Chow, B T *ibid* 1953, 202, 445
8 Wright, S Applied Physiology, pp 844-853, 913 London, 1952
9 Binkley, F , Christensen, G M *J biol Chem* 1951, 192, 575

vation of the hexokinase system, B_{12} may be synergistic with insulin in this step

2 Vitamin B_{12} may favour transformation of glucose to glycogen, in a way which may or may not be similar to that of insulin, as suggested by improvement in the intravenous glucose-tolerance curves

3 Vitamin B_{12} may have an insulin-like action, because it abolishes hyperglycæmia induced in rats by administration of large amounts of glucose (which exhausts the islets of Langerhans)[9]

4 Vitamin B_{12} may antagonise some of the metabolic effects of corticosteroids on carbohydrate metabolism,[10 11] for it reduced the hyperglycæmia induced or aggravated by prednisone in man and improved both the glucose-tolerance curves and insulin-sensitivity test

A E DARWISH
M ESSAM FIKRY

Department of Medicine,
Alexandria University

SAFETY IN PROSTATECTOMY

SIR,—I was disappointed to find no reference to the late Wilson Hey in your leader of May 3

He first adopted immediate operation for all cases in 1940 and worked on the idea until his publications of 1945 and 1946 (*British Journal of Surgery* and *British Medical Journal*), in which he colourfully disposed of all catheters and preliminary drainage These papers caused immense interest, and Professor Wells was outstanding in adopting the heresy, although I notice here he mellows the message and gives these words to another "more patients die by the catheter than by prostatectomy" Wilson Hey would never have said that "every patient", he would have said, "dies by the catheter, and none by my prostatectomy"

If he had been right, and if preliminary drainage was deadly, his "immediate operation" would have been a remarkably brilliant introduction, but adopting the method without reservation at Ancoats Hospital I found that in a series of over 300 cases the retained patient beyond seventy years of age carried a heavy risk with urgent operation, overwhelmingly heavy in comparison with his coevals without retention, and his juniors with or without retention practically all the mortality was crammed into this one group

It seems to me, therefore, that McEachern's reaction to preliminary drainage is necessary only for this older patient with retention, and I would be sorry to see a complete surrender of Hey's doctrine and its attractive simplification of method

Manchester OLIVER JELLY

DEATH OF A BOXER

SIR,—In Dr Lyburn's long and distinguished career in the ring I am surprised that he cannot recall cases of cerebral injury

In hospital outpatients, as a student, I saw a case of subdural hæmorrhage in a professional boxer, and was told later that he had died Our school instructor's son neglected a medical warning to give up his professional career and became blind. Among ringside habitues Dr Lyburn must have met the odd punch-drunk, a victim of repeated minor trauma

In the amateur world damage is not likely to be as serious, a rough calculation shows that in five years at school and hospital I must personally have had between one and two hundred blows hard enough to stun momentarily without dropping, in addition to not a few heavier ones, without the production of any gross dementia now Looking back, perhaps I should have had my head examined!

There was the occasional man hazy for a while after a bout I remember two amateur light-heavies carried from the ring with concussion of longer duration than the ten second knock-out In both confusion and amnesia lasted for days Similar injuries, of course, occurred in team games, but in a smaller proportion of participants

It is the possibility of insidious blunting of the intellect which is the danger, but of which there is no present evidence (except in the punch-drunk) If there are intelligence tests delicate enough to detect any deterioration, perhaps the testing of a series of boxers at the beginning and end of their careers would produce the evidence, for or against, required by Dr Byrom

Ilford, Essex R N COMPTON SMITH

STAPHYLOCOCCAL INFECTIONS IN HOSPITAL

SIR,—In your leader of May 17 you wisely draw attention to the high incidence of staphylococcal infection and the danger of cross-infection in hospital practice

All conscientious clinicians are greatly concerned about this problem but we would wish to disassociate ourselves completely from your suggested remedy—the appointment of a hospital infection officer The British medical profession has been nationalised but there is no reason why we should follow the Civil Service procedure of creating new posts in order to share out responsibilities which are, or should be, already adequately covered Nor do we require to follow the fashion of today, medical and otherwise, of looking westwards across the Atlantic before we make our own plans

It would be pertinent to inquire who would be appointed to the post you suggest a man senior in years and of consultant status Is he to be a clinician, a bacteriologist, an epidemiologist, or a rare hybrid with unusual experience in all three? Do you suggest that this infection officer should conduct an inspection of the hands and nails of the hospital staff like a major-domo examining kitchen boys, or would you wish him to advise consultants on the proper management of their medical and nursing staffs? The consultant in charge should not need to be told what is happening in his unit, he should know for himself when and where infection exists Nurses with boils on the nose do not remain on duty because the medical staff do not appreciate the danger, but because of the gross shortage of nurses

The prevention, investigation, and control of infection in any part of a hospital is surely the direct responsibility of the clinician in charge of that section, working in cooperation with the bacteriologist, whose duty it is to keep a watchful eye on all forms of cross-infection, and constantly to exercise his detective qualities in tracing any source or possible source of danger The introduction of a third party in the person of a "hospital infection officer", can only create a barrier between clinicians and the hospital bacteriologist and prevent that close collaboration which is essential

Hospital medical staffs are fully aware of the dreadful state of affairs which permits the washing of bedpans in patients' baths, the prolonged use of contaminated curtains, inadequate washing and toilet facilities, and out-of-date theatre equipment These problems should be tackled by the administration acting on the advice of the medical staff, which should be fully represented on the hospital house committee

The efficiency and safety of hospital sterilising procedures is the day-to-day concern of the bacteriologist who should have access to wards, sterilisers, operating-rooms, toilets, laundries, &c. If this does not provide the whole answer, and if the higher flights of ecology, pathogenesis, immune relationships, and variability of staphylococci are the important matters, then surely these are also the concern of the hospital bacteriologist who is perfectly competent to deal with them

The present dangers of staphylococcal and other infections constitute a challenge which must be met by the clinicians in direct charge of their patients We most emphatically believe that the appointment of a hospital

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[10] McArthur, J W , Gautier, E., Swallow, K A , Godley, A , MacLachlen E A , Terry, M L , Hume D , Crepeaux, G , Simone, F A , Kestel, H *J clin Invest* 1954 33, 437

[11] Wartham, I T , Headstream, J W. *Diabetes*, 1954, 3, 367

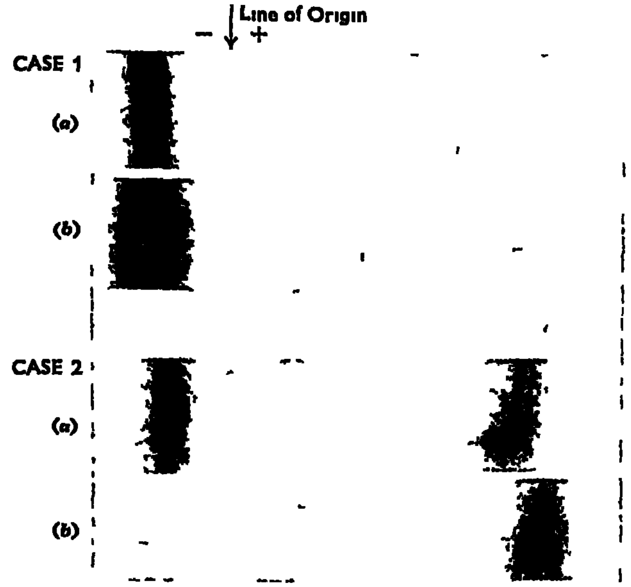
infection officer would achieve nothing, would add confusion to a difficult problem, and would constitute another memorial to the ancient cult of "passing the buck"

Stobhill General Hospital,
Glasgow, N 1

JOHN HUTCHISON
JOHN S STEVENSON

UNUSUAL URINE PROTEIN IN MYELOMATOSIS

SIR,—Cummings[1] reported three bands in the gamma-globulin region of urine proteins in a case of myelomatosis We have observed two bands in this region in case 2 (see accompanying figure), although myelomatosis generally gives serum- and urine-protein patterns as in case 1 The smears from the sternal bone-marrow in case 2 showed numerous plasma cells and "grape cells", as described by Stich et al[2]



Serum and urine proteins in 2 cases of myelomatosis *a*, serum, *b*, urine

Biochemistry Department,
Madras Medical College,
Madras, India

NINAN VERGHESE

REVERSAL OF SUXAMETHONIUM PARALYSIS WITH NEOSTIGMINE

SIR,—In 1952 I reported[3] a case of reversal of suxamethonium-chloride paralysis with neostigmine Since then I have not had a case of prolonged apnœa until last month, when I anæsthetised two sisters, aged 9 years and 7 years, for tonsillectomy

Both children received premedication of 'Omnopon' and scopolamine appropriate for their weight, both were induced with hexobarbitone and suxamethonium bromide, and maintained on N_2O and O_2 The younger child at the end of her tonsillectomy, unlike her sister, was not breathing spontaneously

During the next half-hour she was given nalorphine, nikethamide, and methyl phenidate ('Ritalin'), with no response By this time it was established in my mind that the apnœa was due to the suxamethonium bromide solely, so I gave her gr $^1/_{100}$ of atropine followed by 2 5 mg neostigmine with almost immediate return of respirations, and no relapse

The relaxant was sent to the manufacturers who reported that it was normal in strength and quality Specimens of serum from both girls were also taken but unfortunately the person to whom they were entrusted for analysis died suddenly and they cannot be traced

Dr Bullough reports[4] a similar case in which he used edrophonium before neostigmine, which makes me think that the risk of prolonging the apnœa by the use of anticholinesterases is not so great as is generally believed, in fact, as Dr Bullough suggests, if the action of suxamethonium is prolonged neostigmine will do nothing but good

Lethbridge,
Alberta

J SHEGOG RUDDELL

NOT SO MUTE

SIR,—With reference to your note of March 29 (p 700), we cannot resist the temptation to point out that American proctologists have not been quite so mute as you believe They have three outlets already

(1) *Transactions of the American Proctological Association*, St Louis (1889–)

(2) *Proctology (and Allied Subjects)*, Chicago (1936–)

(3) *American Journal of Proctology* (International Academy of Proctology) (1950–)

And now there is a fourth Librarians have long wished that the unnecessary proliferation of medical journals would cease

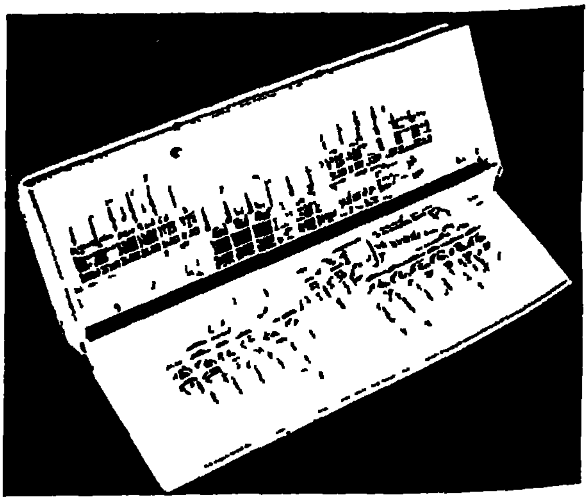
University of British Columbia,
Vancouver

M DOREEN E FRASER
Biomedical Librarian

PORTABLE CONTAINER FOR AMPOULES OF VARIOUS SIZES

SIR,—The ampoule container in the accompanying illustration was designed primarily for the anæsthetist It enables him to have ampoules of various drugs immediately accessible, and has the advantage that when ampoules have been used the empty space is apparent, the drug used can be replaced, so that the necessary drugs are always available

The container, which is made of pressed steel, is about 12 in long, 4 in wide, and 4 in in depth It can be opened at either side, ensuring that the ampoules are easy to remove It holds twelve 2 ml ampoules, eighteen of 1 ml, and two each of 4 ml, 10 ml, and 20 ml—a total of 36 ampoules



Container for ampoules

The case is made by Luckham Ltd, 591/3, Kingston Road, London, S W 20 I am indebted to the photographic department of the Institute of Orthopædics, 234, Great Portland Street, for the illustration

London, W 1

G K T ROCHE

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[1] Cummings, A L *Lancet*, 1957, i, 598
[2] Stich M H, Swiller, A I, Morrison, M *Amer J clin Path* 1955, 25 601
[3] *Lancet*, 1952, ii, 341
[4] *ibid* 1957, ii, 801

PHYSICAL CHANGES IN THE PROLAPSED DISC

SIR,—You were good enough to publish an annotation (June 7) on the difficulties of understanding disc disorders I wonder if you could not have another on the difficulties of understanding Mr Charnley's hypothesis (June 14)

My first objection is to his calling it simple, and my second that it introduces a series of unnecessary postulates Doubtless (I paraphrase his words) he could state that the slow physicochemical changes of normal senescence are symptomless and the elderly person is much more prone to an attack of incomprehension than those of middle age Nevertheless may I suggest a simple scheme which does not require a biochemist or a biophysicist to reassure the practitioner, so that he can reassure the patient by explanation of his symptoms (1) discs wear out, (2) discs are liable to injury, (3) injured or degenerate discs are more liable to injury

Lumbago is a painful muscle spasm which protects a damaged disc from excessive pressure, and prevents further injury or displacement of tissue It is proportional in severity or duration to the degree of disc inefficiency

(1) Minor disc injury = mild lumbago, cured by fibrous tissue repair (2) Major disc injury or degeneration = acute lumbago, often accompanied by œdema around the disc and subjective disturbance of nerve-root function, repairing slowly, and leaving occasional nerve-root adhesions (3) Acute prolapse of degenerate disc material due to movement, or of normal material due to severe trauma, produces the fulminatingly acute syndrome of the prolapsed intervertebral disc

Need we assume that it is necessary to have a raised internal tension in the disc, due to water absorption by mucoprotein, which to fit the theory must be undegenerate, when we have the weight of the body and the force of injury as adequate substitutes? And why must the poor disc be made to go through "the physical changes of senescence in a matter of days or weeks" to explain acute lumbago? Changes in osmotic pressure may play a part in disc physiology, but need we invoke them to explain disc protrusion and lumbago? In short, if this is Mr Charnley's creed I remain apostate

London, W 1 J G BONNIN

THE TOURNIQUET

SIR,—Your leader on the tourniquet (May 31) is timely and interesting but has, I think, at least one serious omission There is no reference to the dangers of the tourniquet in the surgery of severe trauma to the limbs Where deep lacerations have produced flaps or portions of tissue of doubtful viability the use of the tourniquet may make all the difference between saving a useful portion of the limb or losing it The use of the tourniquet in such cases to make primary repair somewhat easier seems indefensible, whether the time of application is short or long

A further point concerns the debridement in this type of case One has seen surgeons attempting debridement with the tourniquet applied Under these conditions it is clearly impossible to assess the blood-supply and therefore viability of the various injured parts Also there is no visible pulsation of the arteries in or near the wound and these can easily be cut in error

The successive turns of the rubber-bandage type of tourniquet are often applied by someone other than the surgeon and can exert a tremendous compression of the limb This must add considerably to the number of painful stimuli transmitted to the brain and even under anæsthesia must aggravate shock

You state that only a pneumatic cuff should be used on the upper limb, but is it not time that a pneumatic cuff large enough for the thigh were introduced and the rubber bandage with all its dangers prohibited?

There should also be a bell, with the impact of a fire alarm, to sound when the tourniquet has been on for 45 minutes

Naturally no surgeon keeps on the tourniquet for longer than the minimum time he requires, and the operations carried out are designed to reduce the risks of infection Nevertheless it seems only logical to support Professor Pannett's contention that where the blood-supply to a limb is stopped for a time the risks of infection are increased

One condition comes to mind where the use of the tourniquet is almost indispensable—a search for a small foreign body in the hand

West Hill Hospital,
Dartford, Kent P DRANSFIELD

OVERSEAS MEDICAL SERVICE

SIR,—As a layman I write with some diffidence on a topic that has been discussed previously[1] in your journal by some distinguished medical correspondents However, I have recently enjoyed two years in the Middle East as secretary of a Government medical department The Government concerned was fortunate in having been able, over the years, to obtain the services of a number of good British doctors, who have done very fine work for the people of the country concerned and who have proved themselves to be "medical ambassadors" of the best type

Whether this high standard of medical service will continue indefinitely is another question During my two years, there were not many applicants for any of the various medical appointments advertised through the British medical press[1] This may have been partly due to the turbulent political conditions in the Middle East, but the biggest difficulty undoubtedly seems to be that, under the present National Health Service system, many good doctors are reluctant to accept posts abroad because of the great difficulties of getting back "into the swim" again should they wish to resume work in this country It seems almost equally evident that a system of secondment, as outlined in your columns by Mr Seddon and other correspondents in 1956, would do much to obviate these difficulties It would also do much to help provide the underdeveloped countries with the improved health services which they so desperately need, and at the same time provide British doctors with better opportunities for periods of service abroad —service which, to judge from some of those who have been abroad, is extremely interesting, enjoyable, and worthwhile

In writing this letter, I do not pretend to be able to add anything to the suggestions made in 1956 However, I am not aware that much progress has been made in this field since then Meanwhile, it is probably fair to say that the situation overseas with regard to this problem certainly does not seem to be improving, and there is greater need than ever for the "medical ambassadors" to whom Mr Roaf referred It seems also to be the case that there may still be "a surplus of good men in the United Kingdom" as Mr Seddon mentioned in 1956

Perhaps the matter could be considered to fall within the terms of reference of the working party recently appointed by the Government to review the problems of medical staffing and manpower

London, S W 5 M C HARDIE

SIR,—The Commonwealth is the Phœnix struggling from the ashes of the Empire May I suggest that from the ashes of our Colonial Medical Service we build a Commonwealth Medical Service directly responsible for its own administration and control to some body representing the countries of the Commonwealth Were the service well run and afforded proper status it should attract capable and experienced men and women

Such a service could be financed by all in the Commonwealth, with the wealthier countries bearing proportionately greater costs Conversely the less-advanced countries would receive most of the services, this would surely be a material and worth-while contribution by the wealthier countries to the less favoured The wealthier countries' gain would be in the greater experience and the wider and more profitable use of their doctors

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[1] Seddon, H J , *Lancet*, 1956 i, 46 Roaf, R , *ibid* p 101 Nassau, E , *ibid* p 205 Annotation, *ibid* 1956, ii, 28

The intangible gains to all nations of the Commonwealth would be great, as such a service would bind them closer Eventually it could even attract new members, thus laying the foundation for a wider and greater Commonwealth, even though it meant finally abandoning the limiting prefix " British "

Department of Health,
Auckland, New Zealand

A S WALLACE
Medical Officer of Health, Auckland

*** The supply of doctors for Colonial territories, which was raised at question time in the House of Commons last week, is mentioned in our parliamentary report on p 1396 —ED L

CARDIAC SYNCOPE ASSOCIATED WITH VOMITING

SIR,—We should like to describe a case of a syndrome similar to that recorded by Dr James (April 12)[1]

A housewife, aged 48, had been admitted to hospital three times and twice extensively examined in clinics because of fainting spells connected with vomiting During one of the admissions, recurrent cerebrovascular accidents were suspected

After such a fainting attack, an electrocardiogram (E C G) showed a short period of 2 1 and 3 1 atrioventricular (A-V) block, during which consciousness was normal (fig 1)

There were no history or clinical signs of heart-disease The vomiting associated with loss of consciousness hinted at the possibility of vagal stimulation as a precipitating factor

Pressure on the right eyeball (while the patient was still connected to the electrocardiograph) caused continuous A-V block (2 1, 3 1, and 4 1) (fig 1*b*) Spontaneous vomiting was followed by loss of consciousness while the tracing was isoelectric except for P waves (rate 38 per min) (fig 1*c*) After a short 2 1 A-V block, sinus rhythm reappeared with lowering of the T wave down to the isoelectric line (fig 1*d*) After several minutes, spontaneous A-V block occurred—with no clinical equivalent, because ventricular contractions were frequent enough (fig 1*f*)

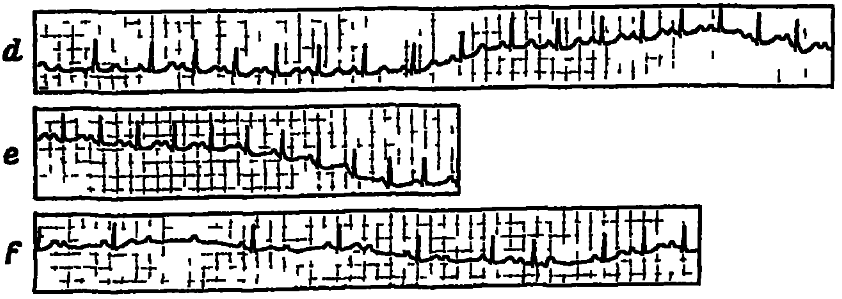

Fig 1—*a*, spontaneous A-V block with subsequent reversion to sinus rhythm, *b*, after pressure on the right eyeball; *c*, *d*, *e*, loss of consciousness with vomiting, *f*, recurrence of spontaneous A-V block

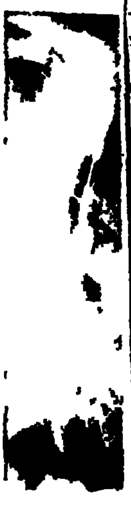

Fig 2—Barium swallow showing œsophageal diverticulum

X-ray *examination of the œsophagus* disclosed a diverticulum of its anterior wall (fig 2) The patient did not relate her attacks to swallowing or drinking, but to vomiting only Neither solid food nor pilocarpine caused attacks An attempt to introduce the metal-olive of a tube into the diverticulum caused no change in the sinus rhythm All other investigations were normal

Treatment consisted in continuous administration of atropine in small doses Three months ago the patient was discharged from the hospital She is well and is still taking atropine

Our patient has no organic heart-disease and thus differs from Dr James' patient Digitalis had not been given, as it had in Correll and Lindert's case[2] Thus, our patient comes closest to the one described by Weiss and Ferris,[1] the first recorded case of which we are aware

In our patient, a vago-vagal reflex was presumably initiated in the œsophageal diverticulum, as in all the three published cases Here, however, neither swallowing nor drinking, but only strong vagal stimulation (such as vomiting or pressure on the eyeball), could elicit the attacks

Hasharon Hospital,
Petah-Tiquah, Israel

J SHAPIRA
N VARSSANO

ACQUIRED OSTEOGENESIS IMPERFECTA ?

SIR,—Osteogenesis imperfecta is generally described as a hereditary affection for which there is yet no effective treatment We have seen no description of a non-hereditary form of this disease, and the following case could be a non-hereditary condition, particularly since efficacious treatment was possible

In May, 1957, I saw a girl, then aged 2 years and 7 months, who had had many fractures due to minor trauma She had previously been examined in a university clinic The report included " blue translucence of the scleræ, skeletal X-rays revealed gracile features The compact layer was very thin Blood calcium, phosphorus and phosphatase values were normal " On the basis of these findings the condition was diagnosed as " osteopsathyrosis " It was subsequently found, however, that the parents were unaffected and that the two family histories included no suspect case of bony fragility

She was a delicate, pale child Apart from excessive flexibility of *all joints* there were a number of signs of dysproteinæmia, such as I had seen in Java during the Japanese occupation Insomnia was severe, the skin dry and withered, and development retarded (height 91 cm , weight 11 5 kg), and there were signs of hypoproteinæmia compensated by dehydration The erythrocyte-count was 5,090,000 per c mm , Hb 94% (Sicca), and a low erythrocyte-sedimentation rate (E S R) 2 mm in 1st hour, 6 mm in 2nd (Westergren) The total blood-protein value was 6 8 mg per 100 ml

Although this case may have been one of osteogenesis imperfecta it cannot be referred to as Lobstein disease, since the hereditary factor was lacking The condition was possibly acquired and symptomatic, in which case it was probably a sequel of dysproteinæmia. In the "hunger camps" of Java adults suffered from osteoporosis with spontaneous fractures as a result of protein (or general) deficiency. An explanation of the hypoproteinæmia in this case might be found in pancreatic insufficiency, since there was considerable creatorrhœa.

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[1] Weiss, S , Ferris, E B *Arch intern Med* 1934, 54, 931

[2] Correll, H L , Lindert, M C I *Amer Heart J* 1949, 37, 446

The girl was treated with a high-protein diet and pancreatic enzyme ('Cotazym' tablets). She was also given injections of the synthetic anabolic *nor*-steroid, nor-androstenolone phenylpropionate ('Durabolin'). The initial dose was $^1/_3$ ml. (about 8 mg.) every two weeks, subsequently reduced to the same quantity once a month. After seven months her appearance had considerably improved, she was alert and active and had shed her fear of falling. The creatorrhœa had disappeared. Body-weight had increased to 15·4 kg. and height to 102 cm. The E.S.R. had risen to 4 mm. in 1st hour, and 13 mm. in 2nd, and the total blood-protein to 7·2 mg. per 100 ml. During the initial period of treatment she still had an occasional fracture under mild strain (e.g., turning while standing on a car seat). Since the seventh month after treatment began, however, she has had no further fractures in spite of increasing activity and playfulness, which involved repeated falls causing swelling and even hæmatomas. The blue discoloration of the scleræ has not changed.

Lochem, Holland. A. K. J. KOUMANS

TREATMENT OF ASTHMA AND HAYFEVER BY HYPNOSIS

SIR,—Having rejected the "intradermal, patch, scratch and prick" tests, we are grateful to Dr. Pepys (June 7) for finally putting us right about the "multiple-pressure" test, which turns out to be only the "prick test" masquerading under another name.

Clearly, publication in your journal has many advantages, not least of which is the subsequent dialectic analysis in the correspondence columns and the varied suggestions as to how future research should be conducted. Not all these, however, are very easy to understand. We learn from Dr. Moynahan (June 14), for example, that in order to find out how suggestion works, we should make controlled studies of random samples of the population. We are under the impression, on the other hand, that such studies would indicate only *if*, not *how*, such treatment works—and, of course, as now stated several times, the therapeutic effects were never under investigation anyway.

As we see it, investigations of the effects of suggestion under hypnosis can only be carried out on hypnotised subjects who respond to suggestion—and the controls should be unhypnotised subjects, or hypnotised subjects to whom no suggestions or different suggestions have been made according to the nature of the experiment. The attempted hypnosis of random samples of the population would show, as is already well known, that 20% can be put into a deep trance, 35% into a medium trance, 35% into a light trance, and that 10% will be unhypnotisable—by any single therapist. 10% of these in turn will fail to react to any attempt at hypnosis by anyone, leaving a hard core of 1% of unhypnotisable individuals in the population.

To carry out our investigations—quite apart from suitable patients, who are rare—we have a rota of about 10 deep-trance subjects, most of whom have been well conditioned to go into a deep trance on the speaking of a single code word, thus saving time otherwise wasted on induction at experimental sessions. These helpful people provide the experimental material with which we operate in our attempts to discover *how*, not if, suggestion under hypnosis produces physical changes in the human body.

In addition we should like to thank Dr. Moynahan for his really timely correction of our reference to what we thought was the von Pirquet paper on "the original allergy." If, as seems to be the case, the allergic response to old tuberculin can be inhibited by suggestion under hypnosis, whatever the mechanism, how many of the other manifestations of allergy included in von Pirquet's *allgemeiner Begriff* might respond as well? We hope to find out.

West London Hospital,
London, W.6.

A. A. MASON
STEPHEN BLACK

RESIDENTIAL CHARGES ALLOWABLE AS INCOME-TAX EXPENSES

SIR,—Dr. Harvey-Smith's successful claim to deduct residential charges as an allowable expense for tax purposes (May 31) is the result of a directive to Inspectors of Taxes following a successful appeal to the General Commissioners of Income Tax undertaken as a test case by the Medical Protection Society.

May I therefore venture to amplify the information in Dr. Harvey-Smith's letter by pointing out that in that case the General Commissioners allowed the appeal because two essential facts were established:

(*a*) The married doctor concerned was *required by the terms of his contract* to reside at the hospital; and

(*b*) *No married quarters* were available for his use, thus obliging him to maintain a separate home for his wife at which he resided during periods of leave.

To be eligible for this concession, therefore, a resident hospital doctor for whose wife no married quarters are provided by the hospital will have to prove to the satisfaction of his Inspector of Taxes that these two conditions exist.

London, W.C.2.

ALISTAIR FRENCH
Secretary, Medical Protection Society.

ÆTIOLOGY OF PRE-ECLAMPTIC TOXÆMIA

SIR,—The crux of Professor Browne's hypothesis (June 14) is that pre-eclamptic toxæmia is caused by deoxycortone (which has not so far been shown to occur naturally), or by another undiscovered mineralocorticoid with similar properties. If any such substance were the cause of pre-eclampsia, it would be reasonable to suppose that a hint of its presence would be reflected in urinary chromatograms in eclampsia. But it is not: in fact, the excretion of formaldehydogenic substances in the urine (which are held to reflect the level of mineralocorticoids in the blood) falls as toxæmia mounts.

Again, overproduction would be expected occasionally in conditions other than pregnancy, unless placental production is alone responsible; but there is sound evidence (from a study of adrenalectomised women [1]) that the placenta contributes barely one-tenth of the corticoids present in pregnancy. The placenta cannot therefore contribute substantially to this hypothetical excess.

The occurrence of eclampsia post partum, and its recrudesence at labour when it had earlier subsided on the death of the fœtus, also indicate that the placenta plays no active role in the ætiology of pre-eclampsia.

Professor Browne holds that there may be no increase in potassium excretion in cortical overactivity; then the absence of an increased potassium excretion in toxæmia when sodium is being retained need not be set against his hypothesis. But that disregards certain data which are impossible to reconcile with his thesis, and which reinforce my view that renal ischæmia is the basis of pre-eclamptic causation—namely, the reduced glomerular filtration-rate, the glomerular ischæmia (proved by renal biopsy), and the presence of vasoexcitormotor substance (V E M) in renal-vein blood of toxæmic women (this substance never appears in the hypertension provoked by corticoids [2])

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[1] Laidlaw, J. C., Cohen, M., Gornall, A. G. *J. clin. Endocrin.* 1958, 18, 222.

London, W 1 JOHN SOPHIAN

FIREPROOF CLOTHING

SIR,—Recently, as part of my training in pædiatrics, I had the opportunity to study a child, aged five years, admitted to hospital with severe clothing burns In the course of this study five shops in South London, specialising in children's clothing, were visited A total of fourteen salesladies was each asked four simple questions

Firstly, they were asked which material commonly used in children's attire was most inflammable Out of fourteen, eight had no idea, two said "flannelette and 'Winceyette'", three said "nylon", and one said "'Tricel'" The work of Colebrook et al [3] clearly shows flannelette and winceyette to be most dangerous whilst nylon and tricel are relatively safe

Secondly, each shop was asked how many customers asked questions about the fire risk of the clothes they bought At three shops the answer was "nobody", at one it was "about one a year", and at the fifth it was "two in nine years' retailing"

Seven of the salesladies knew nothing about the 1954 Fireguards Act, and seven knew of it although most had only a vague idea of its details

Somewhat surprisingly, nearly all knew of the £10 fine applicable in certain cases to parents whose children suffer burns in the home

The impression was gained that a large majority of those questioned had relatively little real interest in advising customers about the safety of the clothes purchased Perhaps this indicates a deficiency in the propaganda directed towards the group of people who retail children's clothing (and probably adult clothing as well) and who are thus best situated to advise their customers about the safety of the articles they buy

Guy's Hospital,
London, S E 1 E K M SMITH

TIME AND THE NERVOUS SYSTEM

SIR,—Those who, like myself, find Professor Woodger's definition of Time (June 7) difficult to grasp, may like to be reminded of the late Arthur Robb's definition This able Irish mathematician surely exhibited a flash of genius when he proposed that Time is simply a matter of "before" and "after" To any ordinary event or experience there are these attributes and Time is the span between them Watches and clocks are useful servants but they involve no master concepts

Bognor Regis SIDNEY RUSS

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[2] Shorr, E Proceedings of the 1st Clinical A C T H Conference, p 314 London, 1950

[3] Colebrook L, Colebrook V, Bull, J, Jackson, D M *Brit med J* 1956, i, 1379

Parliament

Proposed Rebuilding of Charing Cross Hospital

ON June 17, on the adjournment, Mr MICHAEL STEWART drew attention to the proposal to rebuild Charing Cross Hospital and Medical School on the site of what is now Fulham Hospital The people of the borough, he said, did not want a teaching hospital, they wanted their own local hospital rebuilt Their objections were that a teaching hospital on that site would provide 800 instead of 950 beds, would only be able to accept some 200 instead of 700 emergency cases a year, would be unlikely to provide a special geriatric unit, would have to draw its unusual cases from a wide area and would thus have less accommodation for the people of the immediate neighbourhood

From the point of view of Charing Cross also he thought that the proposal had disadvantages The Harrow site, originally suggested for Charing Cross, had 47 acres, instead of 9 acres at Fulham, it took as long to travel by underground from Central London to Fulham as to Harrow The medical school had said that the Harrow site would not provide adequate teaching facilities, but surely the needs of the citizens of Fulham must be considered as well as the needs of the medical school

Mr RICHARD THOMPSON, parliamentary secretary to the Ministry of Health, said that it was clear that the shift of population of Greater London required some decentralisation of the hospitals which serve it This meant the development of hospital services in outer London and the reduction of the former concentration in the centre Hence it was that successive Ministers had accepted the Harrow scheme, and the Charing Cross rebuilding was selected in 1955 as a major project for early progress But because of the strong views of the University of London and the University Grants Committee that the Harrow scheme should be reconsidered in the best interests of medical education, the Minister felt bound to seek an alternative solution Many possibilities were reviewed, and last summer the site of the present Fulham Hospital seemed to provide a reasonable possibility There was an urgent local need for improved hospital facilities, and the demolition and rebuilding of the existing Fulham Hospital, which was badly damaged during the war, had already been agreed upon From the medical education angle the site of the Fulham Hospital was closer to the university than Harrow, and within easy reach of the science departments of the university It was also within the administrative boundaries of the County of London, thus conforming to the statutes of the university

The new scheme involved the rebuilding of Charing Cross Hospital and Medical School on the site of the Fulham Hospital The rebuilt Charing Cross Hospital would eventually replace the existing Fulham Hospital, Fulham Maternity Hospital and the West London Hospital The early regrouping of hospitals would take place, so that the board of governors of the regrouped Charing Cross Hospital could start work in Fulham

Discussions had taken place with the hospital authorities, all parties agreeing in principle to the proposal The South West Metropolitan Regional Hospital Board's agreement included provisos that the new hospital should provide district hospital services comparable with those proposed under the board's earlier plans for redevelopment of the Fulham Hospital and that the position of the existing staff should be safeguarded The board of governors had given assurances that a service fully adequate to the needs of the Fulham area would be provided and that it would accept the transfer of all the staff

Turning to the objections raised in Fulham, Mr Thompson said that the modern tendency was to provide a greater variety of patients for teaching purposes to familiarise students with normal cases as well as the more complicated ones which were formerly sent to teaching hospitals, and there was no reason to think that a teaching hospital could not provide a district service while fulfilling its teaching function A teaching hospital accepted patients from the Emergency Bed Service although its strict liability to do so did not go so far as that of the non-teaching hospital But in an emergency he was certain that we could rely on the hospital to help in every way possible

It was proposed that the new Charing Cross Hospital should replace Fulham Hospital with 382 beds, Fulham Maternity Hospital with 28 beds, and the West London Hospital with 238 beds, giving a total of 648 beds which ultimately would be closed The board of governors had in mind a hospital with 700 to 800 beds, with the usual range of specialties This would mean ultimately that the present total of 648 beds in the Fulham hospitals would be replaced in stages by about 750 It was proposed that 10% of the total beds should be allocated for the chronic sick which would give 70 or 80 beds That was slightly lower than Fulham's present allocation The regional board recognised the need for more beds for the chronic sick and discussions had taken place about where these might be provided

The Minister did not rule out a public inquiry, but he was not convinced that it was the best way to proceed It would entail considerable delay and expense and might not establish many facts or points of view not already known The proposals had been under consideration, and discussions had been going on since last summer, and the Minister hoped to come to a decision fairly soon

National Insurance and National Assistance Tribunals

On June 19 Mr R E Prentice moved the annulment of new regulations concerning the procedure before these tribunals The changes made by these regulations were, he said, changes of detail, but they raised points of importance One change related to legal representation before local appeal tribunals "Any person may be represented by some other person whether having professional qualifications or not " This was a fairly big departure from the existing position At the moment, in cases under the Industrial Injuries Act a claimant might be represented by a legally qualified person with the leave of the chairman, but under the National Insurance Act there was at present no provision for a lawyer to represent a claimant If it became common for lawyers to argue cases before these tribunals, the atmosphere of the tribunals might be damaged There was a tendency for a barrister to arrive with a rather wordy brief and to use legal terminology which was not often understood by his client or by some of the non-legal members of the tribunal The whole attitude of the tribunals might alter even towards claimants who were not legally represented, and we should damage the informal atmosphere People might get the impression that to succeed they needed a lawyer People who could not afford a lawyer and who lost their case might feel that if they had had one they would have succeeded

Mr Prentice also criticised another proposed change "Every hearing by a local tribunal shall be in public except so far as the chairman of the tribunal may otherwise direct if he is of the opinion that intimate personal or financial circumstances may have to be disclosed or that considerations of public security are involved " The National Insurance Advisory Committee had said that hearings should be in public unless the claimant insisted on a private hearing The regulations suggested that the chairman should decide whether or not a hearing should be in public, and the Advisory Committee thought that the claimant should have the last word Mr Prentice believed that the committee's reasoning was sound

Mr John Boyd-Carpenter, Minister of Pensions and National Insurance, referred to "the somewhat anomalous position which has existed so far" It had been the position that a claimant before a National Insurance tribunal could be represented by a friend, provided that the friend had no legal qualifications There was one case when an elderly widow who desired to be represented before a tribunal by her son was unable to do so because her son happened to be a qualified solicitor He did not believe there was any reason to assume that the right to legal representation would be very freely exercised in only the exceptional case would a lawyer appear professionally

It was not realistic, he added, to believe that the opening of the tribunals would cause immense flocks of the public to queue up to attend The Minister held very strongly that justice was much best done in public, and abuses or suspicion of abuses were much better prevented if judicial bodies did their duty in public where the Press could report what was done, and where if anything was done amiss, newspapers, the public, and members of parliament could take the necessary steps There were circumstances in which someone might genuinely be deterred from going to the tribunal if he felt that intimate and personal matters might be brought out in public, and that was a problem which to some extent faced those who attended courts of law, where closed sittings were very exceptional

At the end of the debate Mr Prentice withdrew his motion

Atmospheric Pollution on Thames-side

In an adjournment debate, Mr Bernard Braine spoke of the continued pollution of the atmosphere by emanations from the Thames-side oil refineries Up to a few years ago South-East Essex had a reputation of having almost the purest air in the United Kingdom Now, although the nuisance was intermittent, it was never far away

Mr J R Bevins, parliamentary secretary to the Ministry of Housing and Local Government, replied "quite categorically" that there was no evidence at all at present that these smells were in any sense injurious to health Nevertheless, he sympathised with those who were assailed by these odours "Our aim, which is, I believe the aim of the oil companies as well—I emphasise that—is to see that everything possible is done to remove the sources of these complaints in two ways first of all, by the more rigorous supervision of the plants and, secondly, by a readiness to deal quickly with any source of smell which may be detected by the local residents"

QUESTION TIME

Cost of Prescriptions

Mr Arthur Blenkinsop asked the Minister of Health what was the average cost per prescription prescribed under the National Health Service as at the latest available date, and the answer was approximately 6*s* 4¾*d* in April, 1958 Was the Minister aware, Mr Blenkinsop continued, that the last figure given, at the end of last year, was 4*d* per prescription less? Was he satisfied that the arrangements made with the drug manufacturers were working properly?—Mr Derek Walker-Smith replied that he thought they were, but he would continue to keep the matter under review He was already giving active consideration to the interim report of the Hinchliffe Committee, and he was in consultation about it

In answer to a supplementary question, Mr Walker-Smith said that an examination of samples in the last year showed that expensive corticosteroid preparations which became available in that year and in 1956 were being increasingly prescribed It was likely that this trend towards expensive preparations had continued

Distribution and Recruitment of Nurses

Mr J Johnson asked the Minister what steps he was taking to ensure that there was an equitable distribution of nurses as between the London teaching hospitals and the smaller provincial hospitals Mr Walker-Smith replied that the problem of distribution generally was before the National Consultative Council on the Recruitment of Nurses and Midwives, and he would consider it in the light of the advice they gave Was it not true, Mr Johnson added, that there were large queues and waiting-lists of young nurses for London hospitals? Would it not be possible to devise a voluntary scheme whereby eclamptic causation—namely, the reduced glomerular filtration-rate, the glomerular ischæmia (proved by renal biopsy), and the presence of vasoexcitormotor substance (V E M) in renal-vein blood of toxæmic women (this substance never appears in the hypertension provoked by corticoids[2])

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Guy's Hospital,
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Mr RICHARD THOMPSON, parliamentary secretary to the Ministry of Health, said that it was clear that the shift of population of Greater London required some decentralisation of the hospitals which serve it This meant the development of hospital services in outer London and the reduction of the former concentration in the centre Hence it was that successive Ministers had accepted the Harrow scheme, and the Charing Cross rebuilding was selected in 1955 as a major project for early progress But because of the strong views of the University of London and the University Grants Committee that the Harrow scheme should be reconsidered in the best interests of medical education, the Minister felt bound to seek an alternative solution Many possibilities were reviewed, and last summer the site of the present Fulham Hospital seemed to provide a reasonable possibility There was an urgent local need for improved hospital facilities, and the demolition and rebuilding of the existing Fulham Hospital, which was badly damaged during the war, had already been agreed upon From the medical education angle the site of the Fulham Hospital was closer to the university than Harrow, and within easy reach of the science departments of the university It was also within the administrative boundaries of the County of London, thus conforming to the statutes of the university

The new scheme involved the rebuilding of Charing Cross Hospital and Medical School on the site of the Fulham Hospital The rebuilt Charing Cross Hospital would eventually replace the existing Fulham Hospital, Fulham Maternity Hospital and the West London Hospital The early regrouping of hospitals would take place, so that the board of governors of the regrouped Charing Cross Hospital could start work in Fulham

Discussions had taken place with the hospital authorities, all parties agreeing in principle to the proposal The South West Metropolitan Regional Hospital Board's agreement included provisos that the new hospital should provide district hospital services comparable with those proposed under the board's earlier plans for redevelopment of the Fulham Hospital and that the position of the existing staff should be safeguarded The board of governors had given assurances that a service fully adequate to the needs of the Fulham area would be provided and that it would accept the transfer of all the staff

Turning to the objections raised in Fulham, Mr Thompson said that the modern tendency was to provide a greater variety of patients for teaching purposes to familiarise students with normal cases as well as the more complicated ones which were formerly sent to teaching hospitals, and there was no reason to think that a teaching hospital could not provide a district service while evident in the cause of charity—for example, to assist the dependants of one who had been unfortunate Himself ndefatigable, he insisted that everybody else should be equally ntiring Loyalty was the keynote of his character loyalty to his school, his university, his hospitals, his Lodge, and, whilst a good hater, friendship was to him a sacred trust He fearlessly expressed his opinion in the interests of truth and justice regardless of personal consequences, through antagonising those who might adversely influence his career

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Mr **E Johnson** asked the Minister if he was aware that there was a shortage of nurses in general hospitals, what had been the trend of recruiting during the past five years?—Mr **Walker-Smith** While there are shortages in some hospitals, there has been a most satisfactory increase in the total numbers of nursing staff during the past five years

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Mr **Arthur Blenkinsop** asked the Secretary of State for the Colonies whether he was aware of the shortage of doctors in the Colonial Service, and what steps he was taking to encourage young doctors from Great Britain to take appointments in the West Indies and other Colonial territories —Mr **J D Profumo** replied I am well aware of the constant demand for doctors in the medical departments of the overseas territories, which the Minister is doing his best to meet Vacancies in the West Indies and other territories are advertised in the professional journals as they are notified In addition, special arrangements have been made to allow applications from young doctors to enter the Colonial Service as an alternative to National Service —Mr **Blenkinsop** Will the Minister consider having some consultations with the teaching hospitals to see whether any kind of guarantee can be given to young men entering for temporary service that their chances of promotion in this country are not thereby spoiled?—Mr **Profumo** That is something I should like to look at

Mrs **Lena Jeger** Can the Minister bring this problem more closely before the Minister of Health, who, not long ago, received a report from a committee which suggested that there should be a limitation on the intake of medical students because of the danger of the profession becoming overcrowded?

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Mrs **Joyce Butler** asked the Minister if he would consider setting up a nutrition department under the auspices of the East African High Commissioner for the purposes of food and food consumption research, diet improvement, and propaganda, and to coordinate the various activities undertaken to counteract malnutrition among children and adults in Uganda, Tanganyika, Kenya, and Zanzibar —Mr **Profumo** replied Coordination of such activities is already the function of the East African Council for Medical Research, under the auspices of the East Africa High Commission services, the East African Institute for Medical Research, and the East African Statistical Department A big contribution is also being made by the Infantile Malnutrition Research Unit run by the United Kingdom Medical Research Council in Uganda with the cooperation of the local and High Commission authorities

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To some people, Sir Arnold Stott typified the flaneur And yet even the least discriminating, inclined to superficial judgment, must have felt puzzled to reconcile this character with a man appointed to the Royal Household, selected as consulting physician to the B E F on the outbreak of the world war, whose services were appreciated by promotion to major-general and the award of a K B E The fact was that a façade of apathy and apparent indifference concealed exceptional ability

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HENRY MANNING PEREIRA

L.R.C.P.E., D.P.H.

Dr Pereira, who died on June 11 at the age of 87, was one of that famous medical team who worked under T. F. Ricketts in the Hospital Ships and River Ambulance Service during the smallpox epidemic of 1900–02. Thereafter he never ceased to practise, and to preach, that great master's teaching on the diagnosis and the hospital management of smallpox.

Because of his characteristic modesty, to the medical world at large Pereira was probably the least well-known member of that team, but those of us who worked under him learned more about smallpox from him than from any other source, and his value, especially to medical officers of health, as a consultant—a real smallpox expert of the Ricketts school—was, of course, outstanding and almost unique.

In addition to his smallpox experience Pereira possessed an exceptional knowledge of diphtheria, enteric fever, and the old type of scarlet fever, gained from years of work in the fever hospitals of the Metropolitan Asylums Board, and when the London County Council took over those hospitals in 1930 he was appointed medical superintendent of the Eastern Hospital at Homerton, where he remained until his retirement.

Pereira was a most lovable man, supremely happy in his family life. There are many of us who will treasure the memory of his friendship.

J. P. M.

PETER PAUL DEBONO

O.B.E., M.D.Malta, F.R.C.S., D.P.H.

Prof. P. P. Debono, who died on June 3 at the age of 67, held the chair of surgery in Malta for twenty-five years, during which by practice and teaching, often in difficult circumstances, he did much to enhance the standard of surgery in the island.

After graduating in 1910, Professor Debono worked for a year in London. Returning to Malta he first took a teaching appointment in pathology and anatomy, and in the 1914–18 war he was associated as pathologist with the Royal Naval Medical Service and the R.A.M.C. After the war he turned to surgery, and in 1919–22 he did postgraduate work in England, first at St. Bartholomew's Hospital, London, and latterly in Manchester, obtaining the F.R.C.S. in 1920. In 1926 he was appointed professor of surgery and senior surgeon of the Central Hospital, Malta. In 1944 he became chief surgeon of the Emergency Medical Services of Malta. He retired from the chair in 1951 but continued to practise until his death. In 1936–39 he had served as a nominated member of the Executive Council of Malta, and in 1947 he was elected a member of the Legislative Assembly, of which he was subsequently appointed Speaker, and served as Minister of Health.

Professor Debono married Miss L. Briffa in 1918, and there were two daughters of the marriage.

J. H. S. writes:

I first met P. P. Debono early in 1943. He was still professor of surgery in Malta and working under conditions such as can never have been experienced by any senior clinical teacher before or since. His “ hospital ” was in a requisitioned building in Hamrun a few miles outside Valletta, and it was an unsuitable place for the care of patients and particularly for those requiring surgical treatment. There were other difficulties too. The shortage of food and, still more, the lack of soap were the cause of skin infections that became epidemic. In the place where I worked with one of his equally talented brothers, Prof Joseph Debono, the unfinished St Luke's Hospital, over three-quarters of the children admitted during the poliomyelitis epidemic had scabies or impetigo or both This sort of thing was enough to daunt the most ardent surgeon But Peter Paul plugged away with indomitable courage not only as a surgeon but as a teacher The men he turned out were extremely good Perhaps they were above average, but they may have gained something from having to work under such grim conditions Debono was a true general surgeon, one of the last to deserve the title, and his versatility was astonishing Nevertheless, he realised that specialisation was becoming necessary, and we talked for hours together about future developments in Malta It was not easy convincing him, but when he finally conceded a point, perhaps grudgingly, there was no going back and one could then count on his help

The Maltese Islands hold an honourable place in the history of European medicine and they have turned out men of distinction, some now working in distant parts of the Commonwealth The little medical school, shockingly housed and always short of money, is part of a university founded at the end of the sixteenth century It is easy to criticise its shortcomings, but our Maltese colleagues are even more acutely aware of them and they point out, not unreasonably, that the Government is directly responsible for the University What should not be forgotten is that men of the calibre of the Debono brothers are but three of its many notable alumni

ERNEST KEITH WESTLAKE

M A, M D Cantab, M R C P

Dr E K Westlake, a senior medical registrar at the Middlesex Hospital, who died in London last week at the age of 33, had done valuable work on chronic bronchitis and emphysema

T S, who was a senior colleague of Dr Westlake when he worked at Chase Farm Hospital, Enfield, writes

After a distinguished academic record and house-physicianship at the Middlesex Hospital, Keith Westlake became my house-physician in 1951 and later my registrar Between these two appointments he worked at the Brompton Hospital, first as a house-physician and then as a research assistant in the department of respiratory physiology Later he was registrar at the Hammersmith Hospital and senior registrar at the Middlesex Hospital He made many contributions to the literature on aspects of chronic bronchitis and emphysema, and whilst with me he passed his M R C P examination and completed his M D thesis, entitled " Disordered Respiratory Function and Carbon Dioxide Narcosis in Emphysema ", for which he was awarded the Raymond Horton-Smith prize in 1952–53 This thesis is typical of him and his work, every page reflects his thoroughness and brilliant clear thinking

He was a quiet reserved man, at times moody, difficult to know well and not given to fine speeches, and it was only on closer acquaintance that one appreciated his fine character, determination, and absolute honesty—this last was the most striking of his characteristics He had a most original and critical mind and a prodigious capacity for work He paid great attention to detail and nothing escaped his keen eye His notes were a model of accurate observation and detail—he left nothing to memory Everything had to be just right, and all doubtful observations or measurements were discarded Once his mind was set on an objective nothing would deflect him from it, and this caused people to think that he was hard—which he was not Although his approach might be called robust, beneath it all he was very sensitive and afraid of hurting people's feelings

It was a pleasure and privilege to work with him The whole hospital staff, nursing and medical alike, were fond of him and admired him for his hard work Since he left this hospital he has often been referred to affectionately by the outpatients

Dr Westlake is survived by his wife and two daughters

BERNARD SUTRO OPPENHEIMER

A.B Harvard, M D Columbia

Dr Bernard Oppenheimer, formerly chief of the medical divisions of the Mount Sinai Hospital and the Montefiore Hospital in New York, who died on June 10 at the age of 81, will be remembered by the many British postgraduate students whom he welcomed to his home One of them, D G J, writes

Dr Oppenheimer combined the qualities of an inquisitive clinical research-worker, a physician with clinical acumen, and a hospitable Anglophile He was associated with the Mount Sinai Hospital for over fifty years as physician, medical service chief, teacher, and scientist, and in 1915 he was responsible for the installation of the first cardiographic laboratory there His contribution to cardiovascular problems would be enough for any single lifetime, but typical of his drive and thirst for scientific knowedge was the way in which his retirement was deferred by the initiation of a large and continuing project on the carcinogenic properties of plastics His wife, Dr Enid Oppenheimer, an English physiologist, was his close collaborator in this programme Their weekend country home was always open to overseas postgraduates, who were encouraged, between sets of tennis, to discuss their research and clinical problems in medicine It was a poor man who came away without some new research idea, a fresh outlook on clinical medicine, and a distinct improvement in his tennis

Diary of the Week

JUNE 29 TO JULY 5

Monday, 30th

UNIVERSITY COLLEGE, Gower Street, W C 1
5 P M Dr J D Robertson Molecular Biology of Cell Membranes
POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W 12
4 P M Dr J F Goodwin Combined Valvular Disease
LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE, Keppel Street, W C 1
5 P M Prof Isidor Greenwald (New York) The History of Endemic Goitre Its Significance for the Ætiology of the Disease

Wednesday, 2nd

UNIVERSITY OF LONDON
4 30 P M (London Hospital Medical College, Turner Street, E 1) *Prof* T Hale Ham (Cleveland) Hæmolytic Anæmia
POSTGRADUATE MEDICAL SCHOOL
2 P M Dr Forrest Fulton Tissue Culture for the Diagnosis of Virus Infections
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P M Dr R V Gibson Atrial Septal Defects
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W C 1
5 30 P M Dr E A Muguerza (Madrid) Carcinoma of the Epiglottis
MEDICAL RESEARCH COUNCIL
5 P M (National Institute for Medical Research, Mill Hill, N W 7) Prof Samuel Graff (New York) Experiments with Continuous Metazoan Cell Cultures

Thursday, 3rd

INSTITUTE OF NEUROLOGY, The National Hospital, Queen Square, W C 1
5 30 P M Dr G Melvill Jones Orientation in Flight
INSTITUTE OF CHILD HEALTH, Great Ormond Street, W C 1
5 P M Sir Macfarlane Burnet (Melbourne) Immunological Aspects of Early Life

Appointments

BRUN, FRANK, M B Lond, F F A R C S consultant anæsthetist, Sunderland group of hospitals
FORBES, R Y, L R C P E, D P H deputy M O H, Slough, and assistant M O and school M O, Buckinghamshire
HUGHES, E M, M B Lpool, D P H deputy M O H, Nuneaton, Bedworth, and Atherstone
REDWOOD, C R M, F R C S part-time consultant general surgeon, Doncaster Royal Infirmary
SOUTH, CYRIL, M B Sheff, F R C S part-time consultant surgeon, St Chad's Hospital, Birmingham
SYROP, SARA, MED DIPL Warsaw, D T M & H, D C H, D P H M O, West Ham

Colonial Appointments

BILLINGTON, V L, M B Cantab M O, Tanganyika
CHATTERTON, J J, M R C S M O, Cyprus
IRANI, S J, M D Bombay, F R F P S M O, British Guiana
MOYES, R W, M B Lond M O, Kenya
ROGERS, VINCENT, M B Lpool, D M R D M O, Sarawak
SEN, S K, M B Calcutta, D P H M O, Trinidad
SIMONS, H R, M B Lond M O, South Pacific health service Fiji
TOLLEY, MARY A T, M B N.Z, M R C O G M O (special grade), Uganda

Notes and News

MEDICINE IN CHINA

AT the annual general meeting of the Royal Society of Tropical Medicine and Hygiene on June 19, Prof A W Woodruff gave some of his impressions of medicine in China, derived from his visit last year with a group of British doctors

Setting the scene historically, he said that the traditional Chinese philosophy had hitherto been one of respect for antiquity and rejection of change, but politically the last century had been marked by corruption, civil war, widespread poverty, and foreign invasions In 1948, the change of regime brought a revolution of ideas, as well as the massive political revolution, which completely reversed the ancient conceptions and trends The industrial revolution was initiated and had been accepted with fervour Part of the Government plan was a comprehensive medical scheme which, though not yet completed, was the eventual goal. But China had fewer qualified doctors than Britain, for a population more than ten times as great, though in rural areas there were large numbers of traditional practitioners sometimes skilled in the use of herbal remedies and full of the kind of unscientific mysterious authority so often found among medicine men in backward countries The authorities made use of these men, gave them some form of instruction in scientific medicine whenever possible, and, instead of antagonising them, drew them into the general organisation. But their day would end, and the output of fully trained medical graduates from the 32 colleges which now give five-year courses (soon, it was hoped, to be made six-year courses) would gradually provide the required numbers The standard in these colleges was high, though to British observers the time spent in studying dialectical materialism seemed excessive.

Postgraduate medical education was conducted at the great Peking Medical College, and here again the standard was high There were various research institutes in Peking, Shanghai, and other places, and the subjects for research included epidemic diseases, industrial diseases, public health, traditional medicine, and specific Chinese problems At Shanghai the enormous problems of *Schistosoma japonicum* infection (11 million people were affected, most of them in the Yangtse valley) were being tackled This disease was taken so seriously, and the treatment and control measures were on so large a scale, that Professor Woodruff thought that it would be overcome more quickly than in other countries where it was endemic

In Chinese cities there were now few dogs and few flies, and it was the mark of a good citizen to be diligent in destroying both, it was therefore equally the mark of a bad citizen to be indifferent, and a bad citizen might have a bad time. The streets and the people were clean, and cleanliness, order, and health were popular The former poverty had largely passed away, partly because the Government gave incentives to production, and the old stranglehold of the moneylender had gone. The Government had established the rule of law, stabilised the currency, and started great schemes of reconstruction and industrialisation which would increase wealth and which were popular they were needed for a population growing at a fantastic rate

The price exacted from the people for these undoubted material rewards was conformity, and this was now given with enthusiasm China might soon be the most powerful nation in the world, and we might hope that the traditional Chinese talent for compromise would lead to a system more tolerant than that of Russia China might look to the West if the inducement was strong enough One way in which the West could encourage such a tendency would be by offering training here for young Chinese graduates in the methods and ideals which we found acceptable Professor Woodruff's message was that Europe and the West should make a vital constructive effort of friendship towards this serious, progressive, and rapidly developing people, for whom we have always had warm regard

INADEQUATE DIETS IN PREGNANCY

LAST year there was a noticeable deterioration in the diets of many women, according to Miss Helen Simpson, dietitian to the Simpson Memorial Maternity Pavilion of Edinburgh Royal Infirmary Miss Simpson, in her report on 1957, says that the deterioration was due chiefly to the slightly increased cost of living and to the higher incidence of unemployment In some cases, although the income appeared to be adequate, hire-purchase commitments upset the balance of the budget Protein foods, being the most expensive, were reduced, and more carbohydrate was eaten to satisfy the appetite The special pint of milk provided at half price for a pregnant woman was often shared with the family Less fruit and vegetables were bought when less money was available The result of this was evident in the increasing number of young women found to be anæmic Many women who were apparently in good health at the beginning of pregnancy quickly became anæmic later In addition to iron therapy, dietary investigation and advice were helpful in these cases

NATIONAL ASSISTANCE BOARD

THE report [1] of the Board for 1957 shows that the number of weekly allowances rose during the year by 56,000 to 1,712,000 (covering the needs of nearly $2^1/_2$ million people) The cost of assistance was £112,200,000 Nearly three-quarters of the 1,712,000 allowances went to supplement national insurance benefits, including 978,000 to supplement retirement pensions and 118,000 to supplement sickness benefit or industrial-injury payments Nearly $1^1/_4$ million of the people receiving allowances were over pensionable age.

Between October, 1956, and the end of March, 1957, about 21,000 people from Hungary sought refuge in this country, and at the peak of activity the voluntary organisations, which undertook the task of receiving them, were using well over a hundred establishments to house them. About 5500 emigrated, mainly to Canada, and others were quickly settled in work and found private accommodation But many still needed room—and often free maintenance—in hostels, and when the money available from a fund raised by the Lord Mayor of London was exhausted the cost of running the hostels was borne by the Exchequer, and the Board took over administration from the British Council for Aid to Refugees on Oct. 1 At that date there remained twelve hostels with 1814 residents, by the end of 1957 two more hostels had been closed and the number of residents reduced to 1427 The net cost to the Board for the three months was about £44,000

BILLY GOES TO HOSPITAL

THIS lively coloured picture-book which the departments of child health and medical illustration of Guy's Hospital have combined to produce should do much to reassure any small patient-to-be In appearance it is cleverly reminiscent of one of the pleasanter weekly comics, and it is full of the everyday details which children enjoy A five-year-old who has studied it on his mother's knee will find a hospital ward welcoming and familiar instead of strange and alarming The enclosed leaflet for parents offers sensible advice about preparing a child for his stay in hospital and explains his special need for visits, small gifts, and postcards while he is there, and for extra affection and care when he returns home

On another page of this issue Prof R. S Illingworth mentions some of the hospitals which have already prepared booklets of this kind for their young entrants, and he asks for more Guy's booklet certainly gives his appeal a flying start

AN ATTRACTIVE SANATORIUM

TUBERCULOSIS is more than a disease it is a philosophy And, like other philosophies, it has its distinctive bibliography (*The Magic Mountain* and *The Plague and I* are two examples) The author of a new novel,[2] *At Doctor Mac's*, may have more in common with Betty McDonald than Thomas Mann, but he has nevertheless made a notable addition to this series

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[1] Cmnd. 444 H.M Stationery Office 3s

[2] At Doctor Mac's By PETER QUINCE London J M Dent. 1958 Pp 277 15s

Doctor Mac's is a private sanatorium, maintained by a kindly physician whose only interests in life are tuberculosis and music His establishment may be run along unconventional lines, but it accomplishes the cure of some difficult cases—patients with emotional as well as physical disturbances Though there is no Peter Quince in *The Medical Directory*, the book has an authentic ring, and its readers will not be surprised to learn that the author has practised both as psychiatrist and chest physician

Doctors, of course, are far from enjoying professional immunity to tuberculosis (Laennec and Withering, Trudeau and Ehrlich, were all constrained to take more than an objective interest in the disease) And every doctor will say to himself, when he has finished this book, "If ever I have to go to a sanatorium, let it be one like Doctor Mac's!"

FILMS ON CARDIAC ARREST AND MASSAGE

SOMETIMES in sudden cardiac arrest transthoracic cardiac massage is either not carried out or postponed while less effective procedures are tried, owing to hesitation to enter the chest, coupled with lack of preparation for such an emergency

A film on *Respiratory and Cardiac Arrest* (16 mm , sound, black-and-white, 15 min , 1945) [1] was made by Dr Geoffrey Organe and Dr I W Magill at Westminster Hospital Though much of the film is still accurate, details of the procedure have since been changed

Dr Claude S Beck has made several films on the subject, his most recent one, *Resuscitation for Cardiac Arrest* (16 mm , sound, colour, 18 min , 1956),[2] is the best at present available

Dr Beck, who delivers a filmed lecture, divides his objectives into restoration of the oxygen system and re-establishment of the heart-beat The emergency lasts until the first has been achieved, and time should not be wasted listening for heart-sounds, taking an electrocardiogram, injecting adrenaline, dilating the anal sphincter, and so on The routine should consist of oxygenation through an endotracheal tube and direct cardiac massage through a submammary incision The second stage can be more leisurely The method of performing cardiac massage is demonstrated on a dog's heart, and a series of pressure tracings show the efficacy of different grasps on the heart and the importance of allowing adequate filling between each compression

A short film on *Cardiac Massage* (16 mm , mute, colour, 2 min , 1956),[1] was made by Mr B B Milstein at the Brompton Hospital, London This is primarily a demonstration of the surgical approach to the heart, and the method of cardiac massage with the pericardium intact, through an incision in the pericardium and finally by bimanual compression of the heart It was made to illustrate a lecture on the subject and is thus less complete than the other films

A new film, *Cardiac Arrest* (16 mm , sound, colour, 17 min , 1958) [1] by Dr John Beard was shown at a recent meeting of the Faculty of Anæsthetists at the Royal College of Surgeons of England

It opens with a lecture by Dr Beard on the role of anoxæmia in cardiac arrest A man is then seen to collapse in an outpatient department The technique of cardiac massage is demonstrated on a rubber heart, and the difference between arrest and ventricular fibrillation is shown on an electrocardiogram The patient is given oxygen from an anæsthetic machine, and, since the carotid pulsation is absent and the pupils are dilated, a pharyngeal airway is inserted

An attendant takes over the positive-pressure respiration while the doctor incises the chest in the fourth left interspace, spreads the ribs, and applies cardiac massage On the arrival of the surgeon, the first doctor returns to the head of the table and inserts an endotracheal tube The second half of the film is devoted to a discussion on methods of restoring the heart-beat Finally, mention is made of the intravenous injection of 50% sucrose solution if recovery is delayed

Royal College of Physicians of Edinburgh

The William Cullen prize, awarded by the college every four years " for the greatest benefit done to practical medicine ", has been awarded to Dr W Melville Arnott, professor of medicine in the University of Birmingham

University of Bristol

At recent examinations the following were successful

M D—H M Leather, Henry Urich

M B , Ch B—R T Marcus, Michael Nicholas, R A Sharpe (second class honours), R A R Abraham, Daphne M Allen, Sarah M Brewer, Barbara A Brooking, John Brunning, R A Bunting, J B Burchill, Mervyn Busson, Joan R Coombs, T O Dada, Philip Dent, S V C Egonu, C C Entwistle, P T Gardner, R A G Huish, G H Hulands, F W Lewis, Susi G Leyton, Alison J McConnell, Yvonne E J Marot, B S Milner, C D Murphy, V P Nagpal, E O Olurin, Glenys R Packer, M I eM Parker, M P Patel, A P C H Roome, M H Seymour, F D Skerrett, J M Slater, Ivor Surveyor, Lip Hing Thean, Umathevan Viswalingam, J T Ward, Juliet M Whitehead, Mary G Wilmot

University of Edinburgh

The following appointments have been made

Mr J J Mason Brown, reader in pædiatric surgery, Dr R H Girdwood, reader in medicine, Mr G D Matthew, reader in obstetrics and gynæcology, Dr W N Morley, assistant in medicine, Dr R S Nagle, lecturer in pathology

University of St Andrews

Dr R E Coupland has been appointed to the Cox chair of anatomy in succession to Prof D Rutherford Dow, who retires on Sept 30 The department is in Queen's College, Dundee, and Dr Coupland will be a member of that college

Dr Coupland, graduated M B with honours at Leeds in 1947, thereafter gaining the M D in 1952 and the PH D in 1954 Following a house appointment in surgery at Leeds General Infirmary, Dr Coupland acted as demonstrator in anatomy at the university, and, after National Service with the R A F , he returned to Leeds in 1950 as lecturer—the appointment which he holds at present He spent a period during 1955–56 in the department of anatomy, University of Minnesota, as assistant professor For some years Dr Coupland has been interested in research into adrenal function and specially the distribution and function of chromaffin tissue He has also worked on the transplantation of endocrine organs and on the histochemistry of the autonomic nervous system He will take up his appointment on Oct 1

University of Dublin

At a recent examination the following were awarded the diploma in gynæcology and obstetrics

F C Das, Gauri Deb, Azima Iqbal Qureshi, Sarah Ramachandran, I Raychaudhuri, S Sarkar

European Society of Hæmatology

This society will hold a congress in Bedford College, Regent's Park, London, N W 1, from Sept 7 to 12, 1959 It will be organised by the British section of the society under the presidency of Dr J F Wilkinson Further particulars may be had from the secretary, Dr Ernst Neumark, department of pathology, St Mary's Hospital, W 2

W H O Executive Board

The Executive Board of the World Health Organisation met in Minneapolis, Minnesota, on June 16 and 17, under the chairmanship of Dr Percy Moore (Canada) The Board established a special account to deal with gifts of smallpox vaccine offered by governments to assist in a smallpox eradication campaign The Board established a committee to be available for consultation with W H O 's director-general in his further negotiations with the International Atomic Energy Agency with a view to concluding an agreement between the two agencies

From July 1, under the National Health Service Contributions Act, 1958, the weekly contribution for the National Health Service will be increased by *6d* for men, *4d* for women, and *2d* for juveniles, with an additional *2d* from the employer in the case of employed persons The new combined weekly rates of National Insurance and National Health Service contributions are set out in leaflet N I 103, obtainable at Pensions and National Insurance offices

CORRIGENDUM *Carnegies Emergency Solution of L-Noradrenaline*—This is made up in ' Snapules ' containing 0 2 mg in 2 ml , and not 2 mg in 2 ml as was stated in last week's advertisement (p 4)

Births, Marriages, and Deaths

DEATHS

LAMBERT —On June 16, suddenly at Crowthorne, John Lambert, O B E M A , M D , late medical officer of Wellington College, aged 78

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[1] Available free from I C I Film Library, Imperial Chemical House, Millbank, London, S W 1

[2] Available free from E R Squibb & Sons, 17/18, Old Bond Street, London W 1

[3] Available free from Mr B B Milstein, F R C S , Brompton Hospital, London, S W 3

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REFERENCES AND ABBREVIATIONS

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